Specific Enzymatic Determination of Glucose in Blood and Urine Using Glucose Oxidase

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Adequate methods for the determination of glucose in biologic fluids based upon its reducing ability are well established. These methods, however, lack specificity since they will detect reducing substances other than glucose. Improved specificity has resulted from procedures designed to remove interfering reducing substances. These measures have been applied most successfully to blood and plasma.

The procedure for the precipitation of proteins introduced by Somogyi[1] eliminates the great majority of interfering reducing substances likely to be present in blood, such as proteins, amino acids, glutathione, phosphorylated hexoses, and others. This, however, does not make it possible to distinguish glucose from other hexoses (such as fructose or galactose) or from pentoses and from such substances as glyceraldehyde.[2] For fluids such as urine where many of the interfering reducing substances cannot be removed by available technics the need for a specific determination is obvious. Fermentation, formation of osazones, and chromatography have proved their usefulness, but being rather cumbersome and difficult to quantitate, have not found access to routine laboratories.

Muller in 1928[3] and Coulthard and co-workers in 1942[4] isolated an enzyme from *Aspergillus niger* and *Penicillum notatum* which had the unique property of specifically catalyzing the conversion of beta-glucose to gluconic acid. This enzyme, which was given the name of glucose oxidase, has been studied extensively by Bentley and Neuberger[5] and by Keilin and Hartree.[6] Glucose oxidase was shown to be a flavoprotein with a molecular weight of 152,000 and an alloxazine-adenine dinucleotide as a prosthetic group.[7]

The reactions involved in the conversion of beta-glucose to gluconic acid are shown in table 1. Beta-glucose is oxidized to gluconolactone while the prosthetic group of glucose oxidase is reduced. Gluconolactone is then hydrated to gluconic acid, which is the end product of the reaction. Molecular oxygen serves as a hydrogen acceptor for the reoxidation of the reduced flavoprotein, and hydrogen peroxide is formed. The accumulation of hydrogen peroxide would inhibit the further course of the reaction and catalase is therefore needed to catalyze its decomposition to oxygen and water. The over-all reaction results in the incorporation of one atom of oxygen into each glucose molecule, and glucose loses thereby its reducing properties.

TABLE 1
Oxidation of glucose by glucose oxidase

β-glucose + glucose oxidase $\rightleftarrows$ gluconolactone + glucose oxidase H_2
Gluconolactone + $H_2O \rightleftarrows$ gluconic acid
Glucose oxidase H_2 + 2 O $\rightleftarrows$ glucose oxidase + H_2O_2
H_2O_2 + catalase $\rightleftarrows H_2O$ + O
Over-all reaction:
Glucose + ½ $O_2 \rightarrow$ gluconic acid

It is apparent that in order to get complete oxidation of glucose, which in solution is usually present as a constant mixture of 36 per cent alpha-glucose and 64 per cent beta-glucose, glucomutarotation of the alpha to the beta form must occur. This procedure is speeded up by the addition of buffer, an elevation in temperature, and more specifically by an additional enzymatic

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factor, present in many glucose oxidase preparations, which has been named glucomutarotase.[8]

Glucose oxidase has been experimentally used for glucose determinations by Keilin,[9] Mann,[10] and Needham[11] in England and by Ashmore and others[12] in this country. In most instances oxygen uptake during the reaction has been used to quantitate the amount of glucose present. Ashmore, however, used the decrease in reducing ability after glucose oxidase action to estimate the amount of glucose present in fluids used for the incubation of liver slices. Recently, Eli Lilly and Co. has perfected a practical semiquantitative indicator paper for quick appraisal of glucose in urine, based on the formation of hydrogen peroxide during the reaction. We have attempted to develop a quantitative procedure applicable to urine and blood and particularly suitable for the specific determination of small amounts of glucose.

REAGENTS USED

Two commercial glucose oxidase preparations were used (Sigma Corporation, St. Louis, and the Takamine Laboratories, Inc., Clifton, New Jersey). Both preparations contained approximately 1,500 glucose oxidase units per gram of dry crude extract and variable amounts of catalase and glucomutarotase. Each new batch of enzyme was evaluated by incubating it with a known concentration of glucose under standardized conditions to insure the presence of adequate amounts of these two catalytic agents.

To prepare the enzyme solution glucose oxidase was dissolved in acetate buffer (20 mg. enzyme per ml. of acetate), shaken, and centrifuged. The clear yellowish supernatant was used for glucose determinations. If kept in solution in the cold or frozen, little activity was lost, but reducing substances were liberated from the enzyme preparation, causing high enzyme blank values. For this reason a freshly prepared solution was used for each set of determinations. Powdered, dry, glucose oxidase preparations were kept for as long as one year without appreciable loss of activity. They should be protected from excess light.

The other reagents used were as follows:

Acetate buffer, *p*H 5.6 (19 parts 0.154 M acetic acid and 181 parts 0.154 M sodium acetate).

Lloyd's reagent (Hartman-Leddon Co.).

Zinc sulfate, 5 per cent.

Sodium hydroxide, 0.5 normal.

Alkaline copper tartrate and arsenomolybdate reagent according to Nelson.[13]

DETERMINATION OF GLUCOSE IN URINE

Refrigerated urine specimens are collected using toluene as a preservative. Urines giving a blue Benedict's may be used undiluted. Others must have appropriate dilutions made.

One milliliter of urine is pipetted into each of two Wassermann tubes and a drop of caprylic alcohol is added to prevent foaming during aeration. To one tube is added 1 ml. of acetate buffer (tube A) and to the other 1 ml. of enzyme solution (tube B). All B tubes are then aerated for 20 minutes at room temperature, preferably not below 22°C. For the delivery of oxygen a glass manifold is used, fitted with rubber tubing in which are inserted #25 hypodermic needles. Polyethylene tubing is threaded over the needles in appropriate length to reach the bottom of each tube, thereby insuring thorough mixing and oxygenation. Two milliliters of distilled water and approximately 300 mg. of Lloyd's reagent are added to both A and B tubes and the mixture is filtered. One milliliter of the clear filtrate is then analyzed for reducing substances according to the method of Nelson.[13] The values obtained from the A tubes represent total reducing substances, while those from the enzyme tubes represent only nonglucose reducing substances.

An enzyme blank containing 1 ml. of distilled water and 1 ml. of enzyme solution, as well as a 0.4 mg. per ml. glucose standard, are carried through the same procedure. The reading of the enzyme blank must be subtracted from the readings of the enzyme tubes, thereby correcting for any reducing substances in the enzyme solution which were not entirely removed by the Lloyd's reagent. The standard will serve as an indication of the completeness of the glucose oxidation and therefore as a daily check on the activity of the glucose oxidase preparation used. By subtracting B from A, a measure of true glucose is obtained. One person can easily handle 30 determinations per day.

DETERMINATION OF GLUCOSE IN BLOOD

Blood is drawn and preserved in bottles containing sodium oxalate and sodium fluoride. One milliliter of fluorinated blood is laked by the addition of 2 ml. of water. One milliliter of laked blood is treated with 1 ml. of enzyme solution and another milliliter of laked blood is treated with 1 ml. of acetate buffer. One drop of caprylic alcohol is added to each tube and the tubes containing enzyme are aerated with oxygen for 20 minutes at room temperature. Deproteinization of both tubes is then carried out with 1 ml. of zinc sulfate

and 1 ml. of sodium hydroxide. After centrifugation, the supernatant is used for determination of reducing substances according to the method of Nelson.[13] An enzyme blank and a glucose standard of 0.4 mg. are again similarly treated.

Corrections and calculations are identical with those described for the determination of glucose in urine. When determinations must be carried out on capillary blood, the following procedure is recommended. One-tenth milliliter of blood collected from the fingertip is added to each of two tubes containing 0.9 ml. of dilute sodium fluoride solution. Two-tenths milliliter either of glucose oxidase or of acetate buffer is added to each tube, and after incubation deproteinization is carried out with 0.2 ml. of zinc sulfate and 0.2 ml. of sodium hydroxide. Five-tenths milliliter of the clear supernatant is then used for the determination of reducing substances, proper adjustments being made in the final volume of the solution for colorimetry to insure adequate optical density.

EVALUATION OF THE METHOD

The results of the incubation of glucose oxidase with varying amounts of glucose and for different periods of time at room temperature are shown in table 2. One milligram of glucose was oxidized within 20 minutes, whereas 5 and 10 mg. of glucose required two hours of incubation at room temperature for completion of the reaction. From this and similar experiments it was concluded that glucose concentrations greater than 1.0 mg. per ml. of incubation sample should be avoided when using an incubation period of 20 minutes at room temperature. A small quantity of reducing substances, probably glucose, amounting to between 3 and 4 per cent of the initial glucose incubated with the enzyme was regularly found to remain at the end of incubation. By raising the temperature 37°C., completion of glucose oxidation could be achieved (table 3). On the other hand, the incubation at lower temperature resulted in a marked increase in the non-oxidized glucose remnant. It is important therefore to control the specific conditions in each instance by incubating a known amount of glucose along with the unknown samples. When maximal accuracy is needed, incubation should be carried out at 37 to 40°C., when glucose oxidation can be expected to go to completion.

Recovery experiments are illustrated in table 4. Twenty, 50, 100, and 200 mg. of glucose were added to one liter of each of two urine specimens which were found to contain 40 and 36 mg. per liter. The recoveries of these small amounts of glucose varied from 86 to 107 per cent. The errors, expressed in milligrams per liter, ranged from 8 to 16 mg. Thirty milligrams per liter, or 3 mg. per 100 ml., can therefore easily be detected and an increase of as little as 20 mg. per liter above the base level can be considered significant.

TABLE 2

Glucose oxidation during incubation with glucose oxidase at 25°C.

Glucose added	Per cent glucose oxidized after: 20 min.	60 min.	120 min.
1 mg. per ml.	94	96	95
5 mg. per ml.	86	93	97
10 mg. per ml.	54	84	97

TABLE 3

Glucose oxidation during incubation with glucose oxidase at varying temperatures

Incubating temperature	Per cent glucose remaining after incubation of 1 mg. with glucose oxidase for 20 minutes
5°C.	9.2
25°C.	4.0
37°C.	1.0
	0
	0.5

TABLE 4

Recovery of glucose added to 1,000 ml. of urine

Sample	Glucose added (mg.)	Glucose expected (mg.)	Glucose measured (mg.)	Per cent recovered
Urine A	None	—	36	—
	20	56	48	86
	50	86	80	93
	100	136	146	107
Urine B	None	—	40	—
	200	240	248	103
			252	105
			248	103
			256	106

The great specificity of this enzyme for beta-glucose has been studied extensively by Keilin and Hartree.[14] In good agreement with these investigators we detected slight activity only toward mannose and xylose. At the end of an incubation period of 20 minutes at room temperature, 6.5 per cent of 0.4 mg. of mannose and 4.2 per cent of 0.4 mg. of xylose were oxidized (table 5). Raising the temperature to 37°C. had no appreciable effect on the oxidation of mannose and xylose.

The total absence of activity toward fructose and galactose should be stressed and is further illustrated by the blood values obtained during a fructose tolerance test (table 6). Fructose was measured with resorcinol

TABLE 5

Specificity of enzyme preparation used

	Per cent of sugar (0.4 mg. per ml.) oxidized after 20 minutes aeration
Hexoses	
Glucose	96
Fructose	<1
Galactose	<1
Rhamnose	<1
Sorbose	<1
Mannose	6.5
Pentoses	
Xylose	4.2
Ribose	<1

TABLE 6

Fructose tolerance test (0.5 gm. per kilogram over 10 minutes) in a normal subject

Time (minutes)	Glucose oxidase method		Resorcinol method
	Glucose (mg. per ml.)	"Fructose" (mg. per ml.)	Fructose (mg. per ml.)
0	46	0	0
10	49	153	157
20	40	65	68
30	49	38	39
40	46	27	25
60	43	19	20

according to Higashi's modification of Roe's method[15, 16] and by the present method using glucose oxidase. In the latter instance it was assumed that under fructose tolerance conditions the nonglucose reducing substances present in blood after glucose oxidase action would mainly represent fructose. The values obtained for fructose by both methods are in good agreement; the advantage of the glucose oxidase method resides in the simultaneous measurement of glucose and fructose. The same applies to galactose and may prove of particular value in this instance, since convenient methods for the determination of galactose are not available.

PRACTICAL APPLICATIONS

The method has been extensively applied in this laboratory and glucose determinations have been carried out in over two thousand urine and blood samples. The daily excretion of glucose by normal subjects and by patients without anomalies of carbohydrate metabolism was found to vary within surprisingly narrow limits.

The figures obtained in 30 normal subjects are shown in table 7. It is of interest that glucose represents a relatively small percentage (averaging 14 per cent) of the total reducing substances present in urine after treatment with Lloyd's reagent. The nonglucose reducing substances, expressed as glucose equivalents, ranged from 218 to 809. The range of glucose excretion from day to day in a single metabolically normal patient is shown in figure 1. During 78 days, while on diets with different carbohydrate content, glucose excretion varied from 10 to 239 mg. per day, with a mean of 108 mg. and a standard deviation of ± 52.6. A glucose infusion of 25 gm. over eight hours was without effect on glucose excretion. In contrast, very significant changes were observed when carbohydrate active adrenal steroids were added to the infusion (figure 2). When 200 mg. of hydrocortisone was infused over eight hours the urinary excretion of glucose during the corresponding 24-hour period rose to 1,900 mg. Fifty milligrams of Meticortandrolone and 10 mg. of Fluorometicortandrolone produced an increase in the urinary excretion of glucose to approximately 1,000 mg. for the corresponding 24-hour period. These results are presented at this time to illustrate the possible usefulness of this para-

TABLE 7

Twenty-four-hour urinary glucose excretion in 30 normal subjects

	"Glucose" as measured by conventional methods (mg.)	Glucose as measured by glucose oxidase method (mg.)	Nonglucose reducing substances (mg.)
Mean	511	72	439
Range	242-845	16-132	218-809

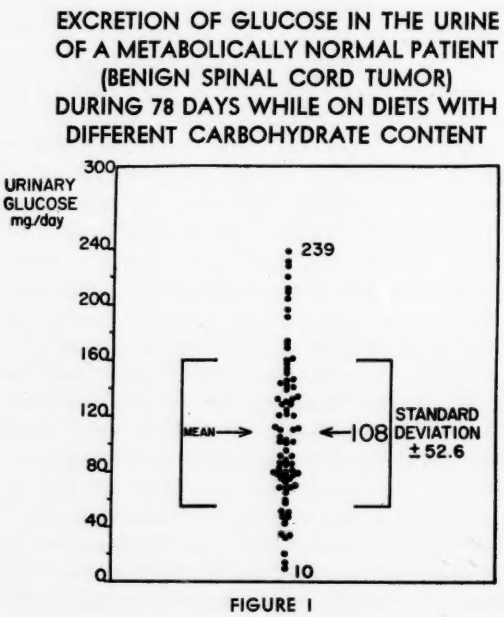

FIGURE 1

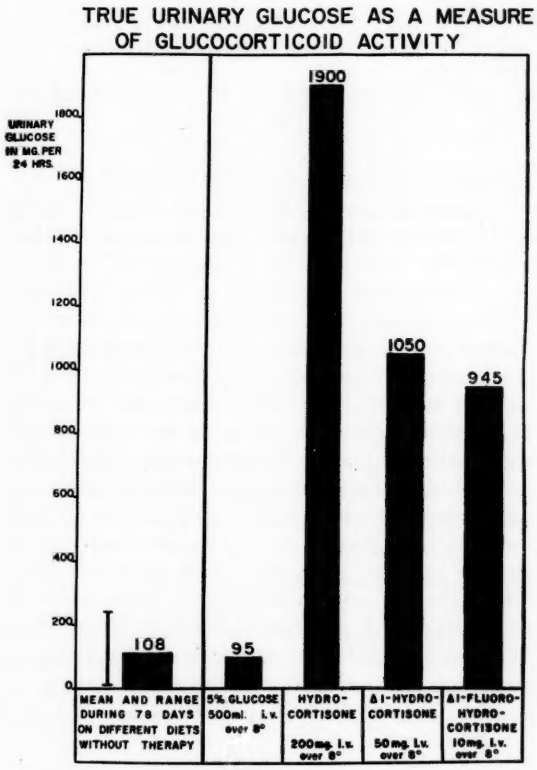

FIGURE 2

meter in the evaluation of hormonal and other effects on carbohydrate metabolism. Such studies are at present being carried out.

SUMMARY AND CONCLUSIONS

A quantitative and relatively simple method for the specific determination of glucose in biologic fluids, using the enzyme glucose oxidase, has been presented. Specificity results from the exclusive oxidation of beta-glucose to gluconic acid by this enzyme. Slight interference might be expected only from mannose and xylose, toward which glucose oxidase shows some activity. The method was found to be especially suitable for the accurate determination of small amounts of glucose in urine and for the simultaneous measurement in blood of glucose and other hexoses such as fructose or galactose during tolerance tests with these substances.

Glucose excretion as measured in 30 normal subjects ranged from 16 to 132 mg. per day, averaging 72 mg. It seemed to be relatively independent of the dietary carbohydrate intake. Significant increases in glucose excretion were observed after administration of carbohydrate active steroid. Glucose excretion as measured by this specific method might prove to be a sensitive index of alterations in carbohydrate metabolism.

SUMMARIO E CONCLUSIONES IN INTERLINGUA

Es presentate un relativemente simple methodo quantitative pro le determination specific de glucosa in fluidos biologic per medio de oxydase de glucosa. Le specificitate del resultatos es conditionate per le facto que iste enzyma effectua un oxydation exclusive de glucosa beta in acido gluconic. Leve incorrectiones pote resultar de mannosa e xylosa, relative al quales oxydase de glucosa monstra un certe activitate. Iste methodo se provava specialmente utile in le determination exacte de parve quantitates de glucosa in urina e in le determination simultanee in sanguine de glucosa e altere hexosas, como fructosa o galactosa, durante tests de toleration executate con iste substantias.

Le excretion de glucosa, mesurate in 30 normal subjectos, variava ab 16 a 132 mg per die, con un valor median de 72 mg. Illo pareva esser relativemente independente del ingestion dietari de hydratos de carbon. Augmentos significative in le excretion de glucosa esseva observate post le administration de steroide active a hydrato de carbon. Le excretion de glucosa mesurate per iste specific methodo va possibilemente monstrar se un sensibile indice de alterationes in le metabolismo de hydratos de carbon.

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DISCUSSIONS

DAVID ADLERSBERG, M.D., (*New York*): Was a comparison made of the effects on these urinary sugars between cortisone, hydrocortisone, and the delta compounds of these hormones?

DR. FROESCH: We have begun such a study, but it is not as yet completed. Preliminary results would indicate that Meticorten exerts four to five times as much glucocorticoid activity as hydrocortisone, while 9-alpha-fluorometicorten is twenty to twenty-five times as potent as hydrocortisone.

RANDALL G. SPRAGUE, M.D., (*Rochester, Minnesota*): I should like to congratulate Dr. Froesch on an excellent presentation.

One question, Dr. Froesch. Did the increased excretion of glucose in response to hydrocortisone reflect an increase in blood glucose; or was it a renal glycosuria?

DR. FROESCH (*closing*): We have tried to assess whether the corticoid-induced enhancement of urinary excretion of glucose is due to an increase in blood glucose level or to changes in the handling of glucose by the kidney. Inulin clearance was measured before and during the acute administration of high doses of cortisone. Tubular glucose reabsorption was found to be slightly depressed and glomerular filtration rate somewhat increased under the influence of cortisone. It would appear that glycosuria results from the combined effects of increased renal glucose load (due to higher postprandial blood glucose levels and a slightly increased glomerular filtration rate) and of decreased tubular glucose reabsorption.

Food Idiosyncrasies

Personal idiosyncrasy will explain many instances in which food is digested with apparent difficulty. This has been repeatedly emphasized by Alvarez. It must be assumed, as this author suggests, that many persons are peculiarly sensitive to some chemical substance carried by an offending food or to its physical state. Else why should canteloupe, for example, disagree as it sometimes does with a person with otherwise excellent digestion, while it gives comfort to another with apparently poor digestion? . . .

The recognition of the particular food to which a person is allergic is not always easy. Cutaneous tests are a disappointment and are seldom to be relied upon. The same applies to other forms of food idiosyncrasy and in this as in many other fields there is no short cut to diagnosis. The use of elimination diets is often of help; but as a rule, painstaking questioning of the patient who has been prompted to intelligent observation brings the best results.

From the book *Nutrition and Diet in Health and Disease* by James S. McLester, M.D., and William J. Darby, M.D., Ph.D. Philadelphia, W. B. Saunders Co., 1952, 6th ed., pp. 141-44.

The Lente Insulins

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The results of chemical, biologic, and clinical studies of the interaction between insulin and zinc were published in 1951 and 1952 by K. Hallas-Møller, P. M. Jersild, K. Petersen, and J. Schlichtkrull.[1-4] It was reported that insulin is insoluble at blood *p*H in the presence of zinc ions, since at this *p*H a slowly soluble and slowly resorbable insulin-zinc compound is formed. The degree of retardation of an insulin-zinc suspension is governed first and foremost by the physical state of the suspended insulin. As seen in figure 1, a suspension of the amorphous modification, Semilente, has a somewhat longer action than ordinary insulin, whereas the crystalline modification, Ultralente, may be compared to protamine-zinc insulin.

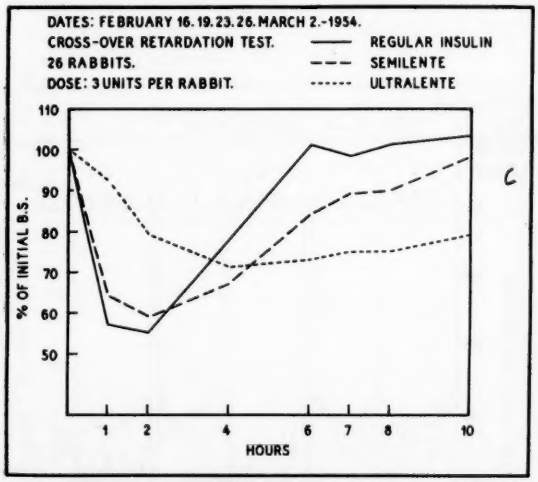

FIG. 1. Means of results obtained in 26 rabbits each given 3 international units of ordinary insulin, Semilente insulin, and Ultralente insulin.

Figure 2 shows, in experiments on 18 rabbits, the relationship between the size of crystals of insulin and the degree of retardation. By a special technic of crystallization it is possible to control the size of crystals, and the figure compares three Ultralente preparations with the crystal size of 5*u*, 20*u*, and 50*u*. The 20*u* and 50*u* preparations give similar blood sugar curves, whereas the action of the 5*u* preparation appears to be of shorter duration. Common practice is to use crystals of about 30*u*.

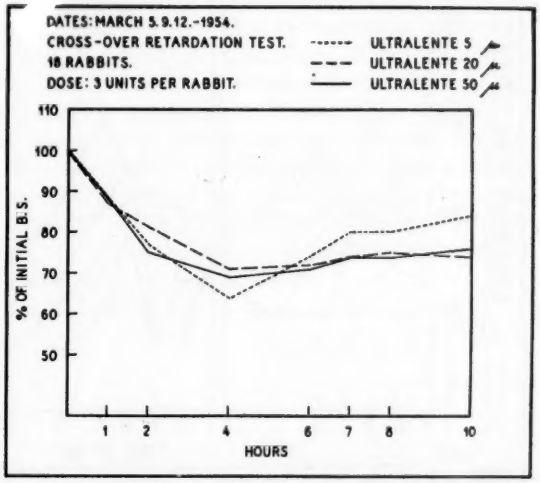

FIG. 2. Means of results obtained in 18 rabbits each given 3 international units of Ultralente insulin of crystal sizes 5μ, 20μ, and 50μ.

In the demonstrated tests, preparations have been used to which had been added 2 mg. of zinc per 1,000 international units. This is the amount of zinc used in protamine-zinc insulin. Considerable variation in the zinc content does not change the action of the Lente insulins. No difference was found in two Ultralente suspensions, the one with 1 mg. and the other with 2 mg. of zinc per 1,000 international units. Figure 3 demonstrates a practical clinical test with two Lente preparations containing 2 mg. and 18 mg. of zinc per 1,000 international units, respectively. This is a considerable quantitative difference in the amount of zinc, but the larger amount retarded the action only a trifle more than the smaller amount. These and many similar experiments established the fact that there was no reason to alter the content of zinc used for so many years in protamine-zinc insulin.

Part of our biologic and clinical investigations with the Lente insulins was directed to show whether the retardation of the insulin effect depended in any way on the species of animal from which the insulin was derived.

Figure 4 compares the results in 24 rabbits given Semilente and Ultralente preparations which were derived

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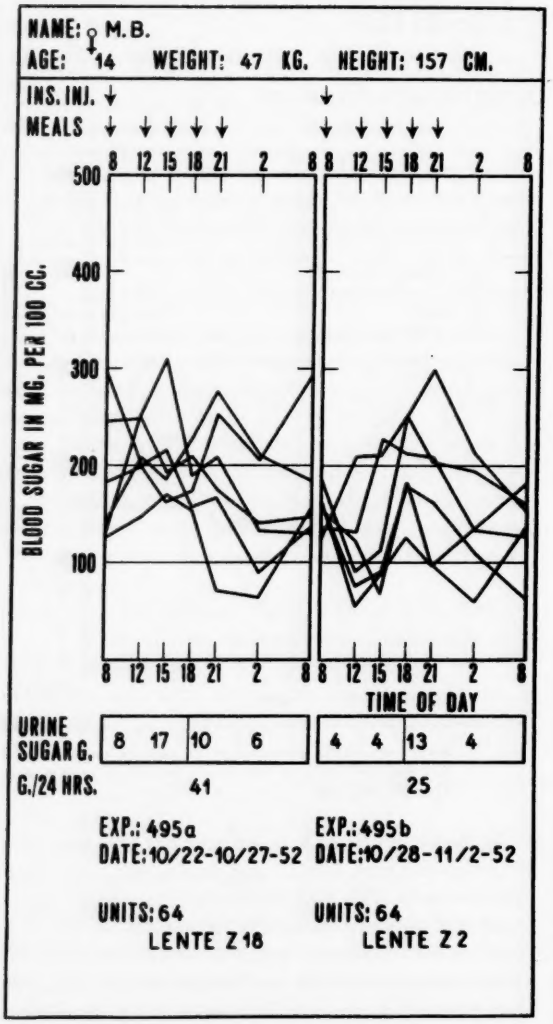

FIG. 3. Comparison of actions of Lente suspensions containing 2 mg. and 18 mg. of zinc per 1,000 international units in diabetic patient.

from ox insulin as well as from pig insulin. It is surprising to see that Ultralente made from pig insulin has exactly the same effect as the Semilente insulins, whereas Ultralente made from ox insulin has the characteristic slow action. In other words, the physical state of pig insulin in the preparations does not affect the degree of retardation in rabbits. This striking result indicates an important fallacy inherent in tests on rabbits, because in diabetics we do not find the same phenomenon. Clinical experiments clearly indicate that the species variation is normally unimportant. It does happen, however, that in a few cases we observe a less pronounced degree of

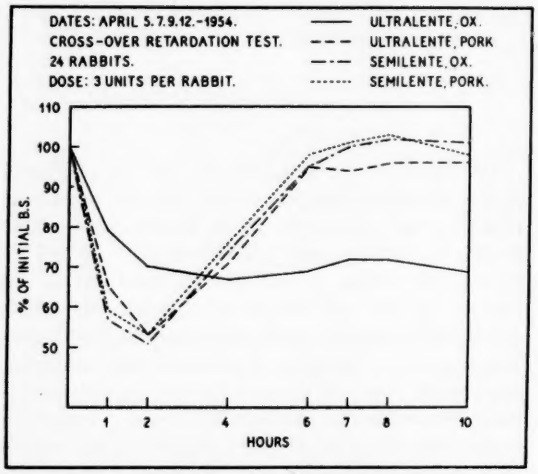

FIG. 4. Means of results obtained in 24 rabbits each given 3 international units of Semilente and Ultralente suspensions derived from pig insulin and from ox insulin.

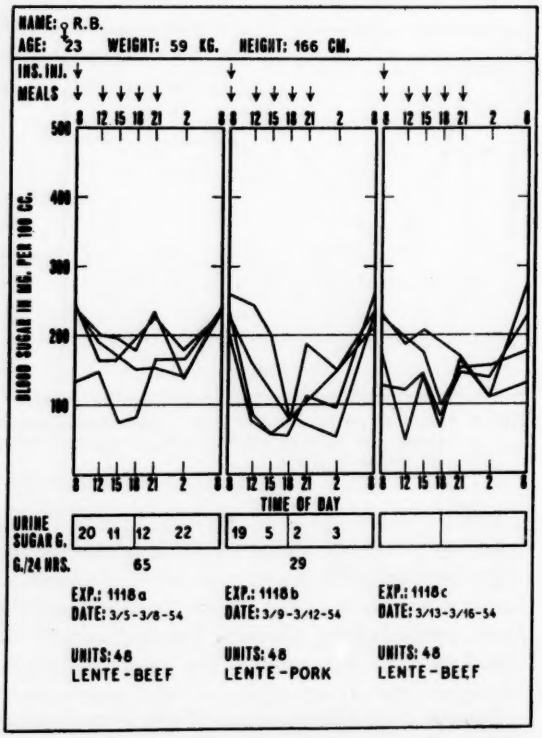

FIG. 5. Comparison of actions of Lente suspensions in which the crystalline fractions were derived from pig insulin and from ox insulin, in diabetic patient.

retardation with pig insulin, which can be seen in figure 5.

The factors which have an influence on the action of insulin-zinc suspensions are easy to control, so that in practice one obtains two well defined, stable insulins, Semilente and Ultralente, with a constant effect. The difference in the action of these insulins is conditioned solely by a physical difference, and they are miscible while retaining the particular effect of the components. Accordingly, a number of mixed insulins can be prepared with varying degrees of retardation.

In recognition of the fact that the action of an insulin is a function of the properties of both insulin and patient, a special clinical test technic has been used for characterizing the different preparations. Figure 6 illustrates the effect of exactly the same depot insulin on three patients with diabetes of almost the same degree. The first patient reacted quickly to the insulin. This type of reaction we call the A reaction. The third patient reacted slowly, and this we call the C reaction. The middle patient reacted satisfactorily to the insulin, there being merely slight 24-hour fluctuations. This we call the B reaction. If an insulin is to be regarded as suitable for administration in one injection during the 24 hours, it must give the highest possible number of B reactions. A large number of patients—excluding those with mild diabetes—are necessary in making such an evaluation.

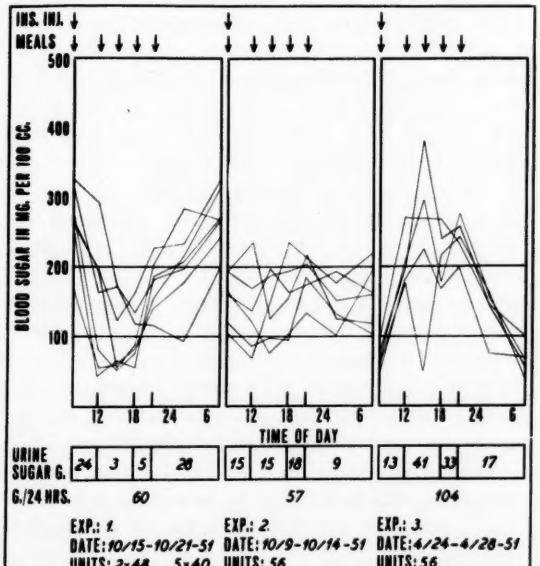

FIG. 6. Results of clinical trials of same depot insulin in 3 diabetic patients showing A, B, and C reactions, respectively. Reproduced by courtesy of "Journal of the American Medical Association."

When a patient has been adjusted to a test preparation of about five to seven days it is generally possible to plot a mean blood sugar curve expressing the patient's adjustment. The upper left half of figure 7 represents five days' treatment of a patient with NPH insulin. Below is the mean curve, which shows an A reaction. The difference between the maximum and minimum blood sugar of the curve—△ BS—indicates the fluctuation. The right half of the figure is a diagram which at the top shows the △ BS, and below the mean blood sugar in 33 cases adjusted on the same insulin. The △ BS columns are drawn below the zero line when there is an A reaction, that is, a fast action, and above it in the case of a C reaction, which means slow action. The individual case illustrated in the left half of the figure recurs in the diagram in the form of the solid columns. The B reaction, the slight blood sugar fluctuations, is identical with only slightly pronounced A and C reactions and therefore corresponds to the small columns.

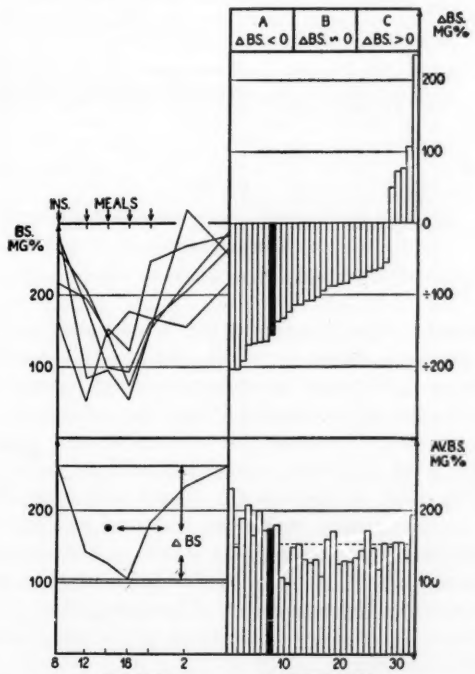

FIG. 7. Diagram for a depot insulin, 33 cases and a descriptive individual case: J. K., age 25, dose 60 units.

It appears from the figure that there is a preponderance of A reactions, which in other words means that the NPH insulin tested here is of a more rapidly acting type of insulin preparation.

In accordance with the technic described here the evaluation was carried out with Semilente (figure 8). As a whole it gives A reactions owing to its relatively short

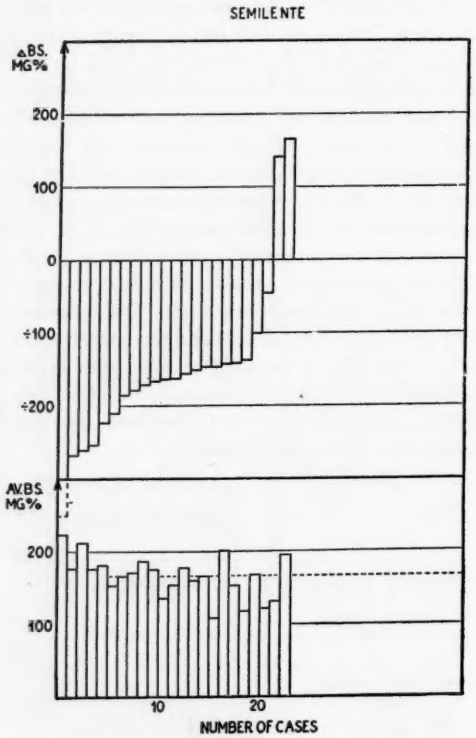

FIG. 8. Insulin Novo Semilente: 23 cases.

range of action. The picture is reversed when Ultralente is employed (figure 9) as this gives mainly C reactions. Figure 10 illustrates the adjustment of 218 patients with Lente, which is a mixture of three parts Semilente and seven parts Ultralente. The material reveals approximately equal amounts of A and C reactions, and a relatively large number of adjustments with small blood sugar fluctuations—B reactions. This must be a prerequisite for the suitability of the insulin as a one-injection preparation. If its degree of retardation were less there would be a larger number of A reactions, and if it were greater the tendency would be to give a larger number of C reactions.

At the Second International Diabetes Congress in Cambridge, England, July 4-8, 1955, J. Schlichtkrull presented a paper dealing with the results of a more elaborate statistical evaluation technic which applies to the patient material upon which this diagram is based. His findings fully confirm the results shown on the diagram. Among other things, he is working with the ratio be-

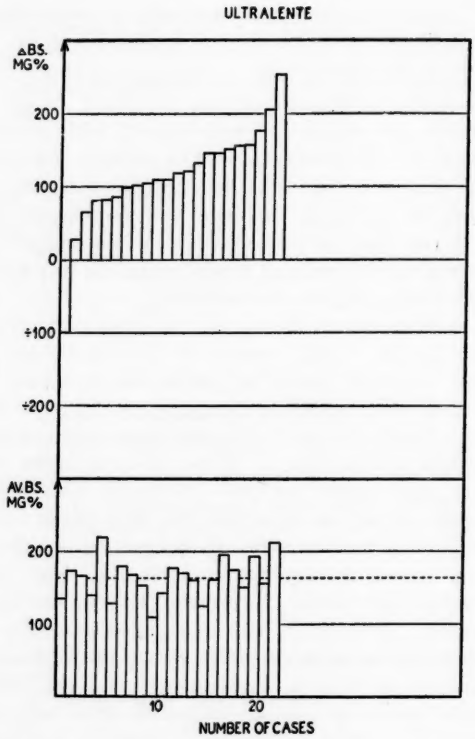

FIG. 9. Insulin Novo Ultralente: 22 cases.

tween the night blood sugar level and the 24-hour level. With a normal physiologic blood sugar curve this ratio will naturally be 1. A low day blood sugar level and a high night level will give a ratio which is greater than 1, corresponding to the A reaction, whereas a high day level and a relatively low night level will give a ratio which is less than 1, corresponding to the C reaction. In figure 11 these ratios—f—are given for different preparations. Lente shows an even share of cases on either side of the unity line, the f value 1. Protamine-zinc insulin and Ultralente show the f value mainly below 1—C reactions. Semilente tends toward A reactions with large f values. NPH likewise tends toward A reactions, as we also saw from the diagram in figure 7.

Here it should be mentioned that we are partly in agreement with Peck[5] when he writes that NPH and the Lente insulin are interchangeable, but we should like to emphasize that Lente has a more marked carry-over effect in the majority of cases. It is a fact, however, that in some cases the action of Lente will be too rapid or too slow, as will be seen from the extreme A and C reactions in figure 10. For such patients Ultralente and Semilente may be mixed with the Lente preparation in order

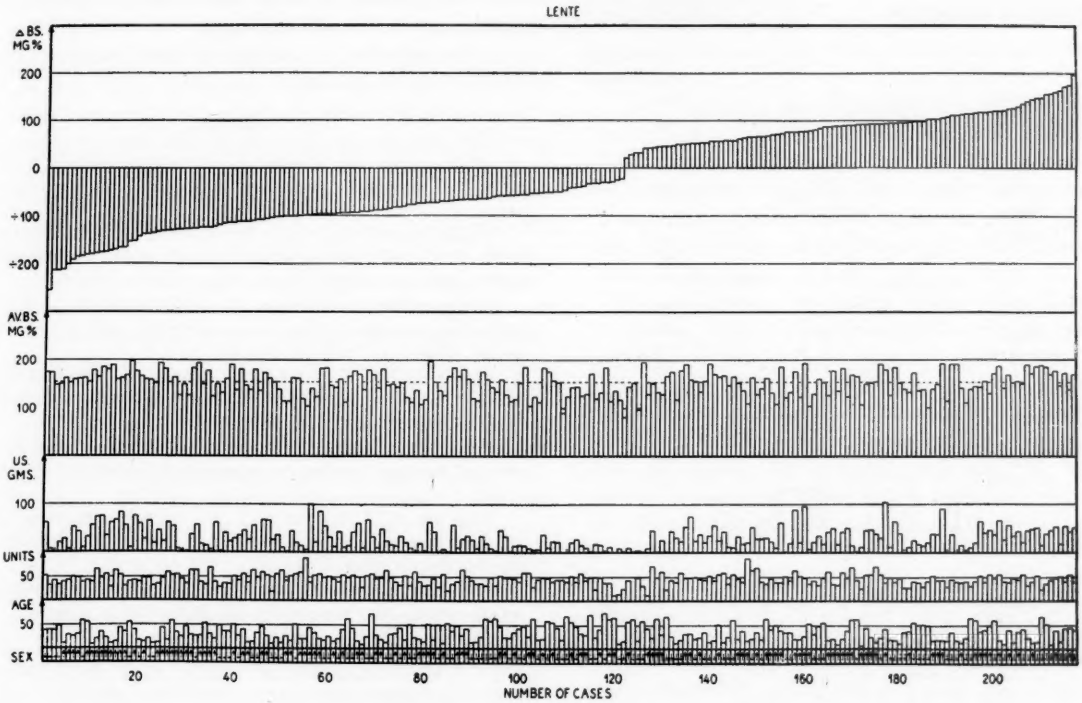

FIG. 10. Insulin Novo Lente: 218 cases.

to prolong or shorten the latter's range of action.

This is the background of the introduction in Europe of the whole Lente trilogy. Through this it is possible for the physician to carry out individualized treatment in difficult cases. In the United States there have been warnings against the advisability of supplementing the number of existing insulin preparations by a further three, as it is feared confusion might arise. We should, however, like to stress that the Lente trilogy is a distinct little family, the members of which can supplement one another in such a simple way that it must be an easy matter to inform the doctors of their right use.

The latest report compiled by Jersild of the Hvidøre Hospital, Copenhagen, states that the number of diabetic patients stabilized on the Lente insulins with an average dose of 40 units daily was 1,030, of whom 990 (96 per cent) were discharged on one injection daily, and 40 (4 per cent) on two injections daily. Of the 990 discharged on one injection daily, the Lente insulins used were Lente-Semilente mixtures in 93 (9 per cent), Lente alone in 790 (80 per cent), Lente-Ultralente mixtures in 100 (10 per cent), and Ultralente alone in 7 (1 per cent).

During the past three years more than 50 publications on the Lente insulins have appeared. Mention should be made of two of the latest, both of which are based on a considerable number of patients. Gurling, Robertson, Whittaker, Oakley, and Lawrence[6] give the results obtained with the use of Lente in the treatment of 479 diabetic patients. They claim that in less than 7 per cent of cases Lente was a failure, whereas 31 per cent of adults and 37 per cent of children previously treated with insulin were found to be improved.

Even more encouraging results were obtained by Stowers and Nabarro,[7] who selected patients for trial with the Lente preparations only if the previous treatment had proved to be unsatisfactory. They clearly demonstrate that a large percentage of these diabetics benefited from the transfer to Lente. Furthermore, the authors state that in the majority of patients Lente—in the ratio of three parts Semilente to seven parts Ultralente—proved satisfactory. Fourteen per cent needed a larger proportion of the Ultralente insulin and 2.5 per cent a larger proportion of the Semilente insulin.

In general, the many clinical publications confirm that our insulin group made the right choice of the Lente composition, and we expect that similar results may be achieved in the United States.

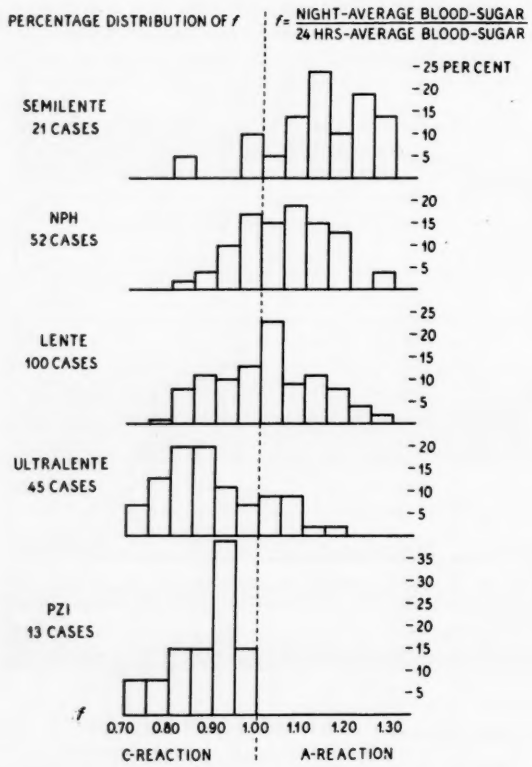

FIG. 11. Comparison between the action of different insulin preparations.

SUMMARY

1. The interaction between insulin and zinc is described with special reference to the physical state and the origin of insulin and the concentration of zinc.

2. A special technic of clinical evaluation and its application to the effects of Lente, Semilente and Ultralente insulins is reported.

3. The treatment of more than 1,000 diabetics at the Hvidøre Hospital, Copenhagen, is reviewed.

4. Results obtained with the Lente insulins in other hospitals are reported.

SUMMARIO IN INTERLINGUA

Le Insulinas Lente

1. Le interaction de insulina e zinc es describite con referentia special al stato physic e al origine de insulina e al concentration de zinc.

2. Es reportate un technica special de evalutation clinic, insimul con su application al effectos de insulinas Lente, Semilente, e Ultralente.

3. Es presentate un revista de plus que 1000 diabeticos al Hospital Hvidør a Copenhagen.

4. Es reportate le resultatos obtenite per insulinas Lente a altere hospitales.

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DISCUSSIONS OF THE ABOVE PAPER BY K. HALLAS-MOLLER, PH.D., AND THE PAPER ENTITLED "LENTE INSULIN: CLINICAL EVALUATION IN 109 DIABETIC PATIENTS" BY EDGAR A. HAUNZ, M.D., GRAND FORKS, NORTH DAKOTA

ALEXANDER MARBLE, M.D., (*Boston*): I think it might be of interest to give a brief summary of our experience with Lente insulin in the last two years during which we have used it in treating sizable groups of patients of various ages.

In general, its action has appeared to be similar to that of NPH insulin and we have used it exactly as we have the NPH type. Substituting it for NPH insulin, unit for unit, we have obtained about the same degree of control of diabetes. In the treatment of patients requiring more rapidity of insulin action than that possessed by Lente insulin alone, we have placed crystalline insulin with it in the syringe just as we have been accustomed to doing with the crystalline and NPH types.

In studies made by Drs. Robert E. Slayton and Ruth E. Burrows of our group with 23 boys at the Elliott P. Joslin Camp, average capillary blood sugar values were obtained every two hours through the day and night with these boys who were leading an active camp life and eating their usual diets. The doses of Lente and NPH insulins in this comparative study were the same in any individual boy. Throughout most of its extent, the composite blood sugar curve following Lente

insulin lay very closely to that following NPH insulin. There was some suggestion that, at least in this group of boys, the Lente insulin did not carry through for quite as long as the NPH variety. However, with other patients not included in this study, the Lente type seemed to act slightly longer than NPH insulin. All told, the effect was about the same.

In 40 cases, crystalline and Lente insulins were given by separate injection on one day and on another day the two types in the same dosage were placed in the same syringe just before injection. The composite blood sugar curves obtained lie very close together. It is true that early in the forenoon following breakfast when the two types were given in the same syringe, there appeared to be not quite as much early, rapid insulin action. Furthermore, later in the day there appeared to be a slightly greater hypoglycemic effect than when the two varieties were given by separate injection. However, the differences in action were small and from a clinical standpoint it is entirely feasible to give crystalline and Lente insulins in the same syringe. It goes without saying that the patient appreciates the convenience of the single injection.

ALVAH L. NEWCOMB, M.D., (*Wilmette, Illinois*): My associates and I have had the opportunity of treating 54 children, and they have all done quite well, except for 9. In nine cases, we had to go back to the former insulin, for different reasons, generally because they were not well controlled; one child developed generalized urticaria, and a second child developed hepatomegaly.

I wonder if Dr. Hallas-Møller has seen hepatomegaly develop. We had not noted it since the days we had been using only regular insulin. The hepatomegaly subsided as soon as the former insulin was prescribed.

We did see some rather severe hypoglycemic reactions under a variety of different situations.

EWEN DOWNIE, M.D., (*Melbourne, Australia*): My experience in using the Lente insulins extends for about 18 months. I do not have any figures with me, but my associates and I have used them in over 200 patients.

I have been interested in the experiences of the previous speaker, in using crystalline insulin with Lente. On occasions when we have experienced difficulty with stabilization, it has been our practice to use extemporaneous mixtures of Lente with Semilente or Ultralente insulins rather than combining regular insulin with Lente.

I should like to direct a question either to Dr. Hallas-Møller or to Dr. Haunz, as to whether they have had any experience in the use of mixtures of Ultralente and Semilente insulins. Has it been their practice to use them in the same way as we use regular and protamine-zinc insulins, varying the proportions according to a patient's needs?

GEORGE W. KOCH, M.D., (*Anaheim, California*): Have you seen any skin reactions after the use of Lente insulin?

LEON S. SMELO, M.D., (*Birmingham, Alabama*): In answer to the question whether Ultralente might be added to Lente insulin, we have added Ultralente to the commercially available Lente insulin and obtained good prolongation of the duration of action of the Lente insulin when this was necessary to secure a normal fasting blood sugar.

THOMAS HODGE MCGAVACK, M.D., (*New York*): Dr. Haunz, with your mixtures of Lente and regular insulin, have you had any difficulty, from day to day or from time to time, in maintaining a smooth, dependable action? In view of the differences in zinc content and *p*H, it would seem to me you could run into considerable trouble. This would be especially true when sufficient amounts of regular insulin are added to bring the *p*H of the mixture to or close to the isoelectric point of insulin.

K. HALLAS-MØLLER, PH.D.: There seems to be a considerable interest in mixing Lente with regular insulin in order to obtain a stronger initial effect.

To tell the truth, as long as Semilente is not available in this country, you are forced to use regular insulin for this purpose. What actually happens is that by mixing Lente with regular insulin, the *p*H will change. Dr. Haunz has told us that, in a mixture of 1:1 of the two insulin preparations, he measured the *p*H to be between 5 and 6. In this *p*H interval, the regular insulin will be converted into an amorphous precipitate identical with Semilente. When this amorphous precipitate is allowed to stand overnight, it will be converted into a crystalline material which means abolition of the desired fast action of the mixture, instead of which you will get a slow-acting preparation comparable to Ultralente.

This is the background for our marketing Semilente in Europe. Semilente has *p*H 7 and can be mixed with either Lente or Ultralente without entailing alterations in the specific action of the components, because no change will take place in the physical state of the insulin. Of course, if regular insulin and Lente are mixed in the syringe and immediately injected as practiced by Dr. Marble, you will undoubtedly get good results. My only comment on this technic is that in the layer between the two kinds of insulin, some crystalline material might be existent in a medium of low *p*H. These crystals might be dissolved and reprecipitated as amorphous material shortening the action of the preparation.

I believe this will explain the difficulties connected with the use of this kind of mixture. On account of our

experience we must strongly advocate that both Semilente and Ultralente should be available.

The foregoing, I think, will also answer the question asked by Dr. Haunz.

I have also been asked about allergy. Of course, there have been a few cases of this nature in the meantime, but I know for certain that there were only 2 patients showing allergy among the 1,030 patients referred to in my paper. Even if the insulin species were changed or the insulin was recrystallized many times, it would be impossible to avoid the rare cases of hypersensitivity reactions indicating true insulin allergy.

In reply to one further question I can say that we have not seen any influence of unknown nature on the diabetic organism which the Lente insulins might induce in comparison with hitherto existing insulin preparations.

Dr. Downie inquired about the use of Semilente and Ultralente. I think his question will be more or less answered by my foregoing statements.

One of the members raised the question of lipo-atrophy. Just before I left Copenhagen, we received the first report of lipo-atrophy in a patient who had been treated with Lente for several years. Generally speaking, I feel that the test period has so far been too short to prove whether the Lente therapy can reduce the frequency of lipo-atrophy observed in previous regimes.

EDGAR A. HAUNZ, M.D., (*Grand Forks, North Dakota*): We have encountered one case of insulin atrophy which occurred in a child eight years old during the administration of Lente insulin.

I think the problem of mixtures of Lente and zinc insulin crystals should be clarified. All our mixtures were made daily and not prepared in advance. Each mixture was made in the syringe. According to what Dr. Marble has stated, we do not mix the preparation after the two insulins are drawn into the syringe. That is unnecessary because they apparently act independently; therefore, it is unnecessary to mix them as you would mix protamine or NPH insulins with unmodified insulin.

Dr. Marble has pointed out in Joslin's textbook that the incidence of skin reactions, as noted by different observers, has varied considerably, and such discrepancies are apparently due to whether or not minor responses are included. We included all responses, I should say, because we kept these patients under very close observation.

In conclusion, it has long been known that the incidence of sensitivity reactions to insulin falls precipitously when the insulin preparation has been recrystallized several times, and for that reason such reactions should be much less frequent when using the new insulin zinc suspensions.

Diabetes and Insurance

Glycosuria has long been a favorite subject for investigation in the insurance field. A current study provides further confirmation of the general benign outlook for mild diabetics. As you all probably know, insurance contracts have been made increasingly available in recent years to well regulated diabetics with no evidence of complications. In the current mortality studies, glycosuria of less than 1 per cent was not attended by any adverse mortality experience, except in older individuals who had some additional impairment such as obesity or elevated blood pressure, etc. Deaths among diabetics were due preponderantly to diabetes itself, diseases of the heart and circulatory system, malignancy and respiratory illness.

From "The Internist and Life Insurance" by Harry E. Ungerleider, M.D., New York, N. Y., *Annals of Internal Medicine* 41:124-30, July 1954.

The Ease and Comfort of Digestion

Psychic factors do not seem to influence the ultimate utilization of food, for Hawk and his associates found that protein prepared in an unpalatable manner was as completely utilized as that which had been more attractively served.

. . . The ease and comfort with which food is disposed of by the stomach and intestine comprise what is easily taken to be digestibility. This depends on many factors, chiefly the secretory and motor response which the food calls forth and a subjective sensation which it produces. The latter is determined in large measure by the former. These several influences in turn are dependent on the physical state of the food, its chemical composition and its appeal to the appetite. In addition to these factors, digestibility is often covered by idiosyncrasy. This follows no law; it is often psychic, sometimes allergic, and not infrequently of unknown nature. . . .

From the book *Nutrition and Diet in Health and Disease* by James S. McLester, M.D., and William J. Darby, M.D., Ph.D. Philadelphia, W. B. Saunders Co., 1952, 6th ed., pp. 136-37.

The Distribution and Metabolism of Insulin Labeled with Radioactive Iodine (I^{131}) in Normal and Diabetic Subjects

George W. Welsh, 3rd, M.D., Elaine D. Henley, M.D.,**
Robert H. Williams, M.D.,† and Neil J. Elgee, M.D.,‡ Seattle

To investigate possible differences in the distribution and metabolism of insulin in diabetics and normals, insulin labeled with radioactive iodine (I^{131}) was given intravenously to 40 diabetics of varying type and severity, 15 healthy controls, and 11 other nondiabetics with various illnesses. The labeled insulin was given in tracer amounts (50 to 100 microcuries) and test doses varied between 0.5 and 5.0 units of insulin. The dose was diluted in normal physiologic saline solution and injected slowly into fasting subjects over a two-minute period. In most cases therapeutic insulin had been withheld from diabetics for 24 to 96 hours. Plasma samples were drawn at predetermined times, and the amount of protein-bound radioactivity was determined by precipitation with trichloroacetic acid (TCA).

Since labeled insulin is virtually completely precipitated with TCA, the protein-bound radioactivity was assumed to represent undegraded labeled insulin, whereas the TCA-soluble radioactivity was assumed to be comprised of the degradation products of the labeled hormone. Total urinary radioactivity, of which an average of 95 per cent is TCA-soluble, was also measured during the test period. In some subjects surface measurement of radioactivity over various organ areas, such as the thyroid, liver, kidney, and muscle masses, was made.

The TCA-precipitable (protein-bound), presumably undegraded, labeled insulin disappeared rapidly from the plasma of healthy controls and nondiabetics with other illnesses. Samples drawn two minutes after intravenous injection of labeled insulin showed an average of only 47 per cent of the dose remaining in the plasma. This rapid disappearance rate continued for 15 minutes, when only 20 per cent of the dose remained in the plasma, and at 60 minutes only 7.7 per cent remained. The resultant curve was reproducible with small variations in all the controls. Nondiabetics with severe hepatic and renal disease, pancreatitis, carcinomatosis, or thyrotoxicosis, receiving steroid therapy, or under anesthesia, gave essentially the same curves as controls. The degradation products in the TCA-soluble fraction of the plasma increased rapidly to an average maximum of 12 per cent of the administered dose in one hour. Urinary radioactivity, over a one-hour collection period, averaged 10 per cent of the dose.

In contrast, 27 of the 40 diabetics showed a retention of undegraded labeled insulin in the plasma, to markedly varying degree, over the one-hour test period. The average retention amounted to 37 per cent of the dose at one hour. Three of these diabetics retained over 80 per cent of the labeled insulin in their plasma.

Thirteen other diabetics, representing one-third of those studied, exhibited no increased retention, and labeled insulin disappeared from their plasma virtually as rapidly as in controls.

There appeared to be no correlation between the abnormally large retention of labeled hormone in the plasma and the insulin requirements, blood sugar, duration of diabetes, degree of diabetic complications, and clinical condition of the subjects. Four diabetics were not fasted and were given their usual therapeutic insulin three hours prior to testing, and two were given intravenous insulin loads fifteen minutes prior to testing. All these subjects still retained large percentages of undegraded insulin in their plasma.

Abstract of paper presented at the Joint Meeting of The Endocrine Society and the American Diabetes Association in Atlantic City, June 4, 1955.

From the Department of Medicine, University of Washington School of Medicine, Seattle.

*Trainee, National Institute of Arthritis and Metabolic Diseases and Assistant in Medicine, University of Washington.

†Executive Officer and Professor of Medicine, University of Washington.

‡Resident in Medicine, King County Hospital, Seattle.

Supported in part by grants-in-aid from the United States Public Health Service, the Atomic Energy Commission and the Upjohn Company.

Urinary radioactivity, plasma TCA-soluble radioactivity, and concentration of radioactivity over the thyroid were significantly less in the diabetics, and were roughly inversely proportional to the percentage of dose of undegraded insulin retained in the plasma. No significant differences in concentration of radioactivity were noted over other organs.

In vitro experiments were designed to show whether the retention of labeled insulin in the plasma of diabetics was due to factors present in or extrinsic to the plasma itself. Human plasma, labeled insulin, and either rat liver slices or quarter diaphragms were incubated together. These tissues have been shown by other investigators to bind insulin rapidly and firmly, and to degrade labeled insulin, presumably by proteolytic action. Perhaps it could be shown that certain factors in human plasma, particularly diabetics' plasma, would bind labeled insulin in such a manner as to deter its entry into tissues, and degradation might be retarded. Using plasma from controls and from diabetics who retained labeled insulin in their plasma in vivo, it was shown that with diabetic plasma there was markedly less labeled insulin bound to the rat tissues in vitro. The greater the amount of labeled insulin retained in the plasma in vivo, the less the amount was bound to rat tissues in vitro. Similarly, the amount of degradation of labeled insulin in vitro was proportionately less in the presence of diabetic plasma.

It is suggested from these studies that there is a factor in the plasma of many diabetics which tends to bind more insulin in the plasma compartment both in vivo and in vitro. This factor could represent an alteration of the normal binding of insulin by plasma constituents, either quantitatively or qualitatively. The retention of labeled insulin in the plasma compartment in diabetics might reflect only binding of insulin to plasma proteins or other components which are "unsaturated" in the diabetic state, due to insulin deficiency. Preliminary experiments with diabetic plasma incubated in vitro with labeled insulin and rat liver homogenate have shown that the prior addition of nonlabeled insulin to the plasma results in *increased* degradation of labeled insulin by liver homogenate. This prior addition of nonlabeled insulin to diabetic plasma may saturate the carriers of insulin and allow more rapid degradation of labeled insulin added later. However, when nonlabeled insulin is added to normal plasma, in a similar system, there is a *decrease* in the amount of degradation, indicating that insulin is present in excess and competing for the degradation system.

SUMMARY

1. Insulin labeled with radioactive iodine (I^{131}) disappears less rapidly from the plasma of many diabetics, as compared with normal controls and other nondiabetics.
2. There is also less rapid degradation of labeled insulin by these diabetics, as compared with controls.
3. There is no apparent correlation between these observations and the clinical characteristics of the diabetics.
4. In vitro studies suggest that in diabetics the "unsaturation" of plasma components with insulin may be responsible in part for the apparent retention of labeled insulin in the plasma in vivo, and decreased binding and degradation by rat tissues in vitro.

SUMMARIO IN INTERLINGUA

Distribution e Metabolismo de Insulina Etiquettate per Iodo Radio-Active in Subjectos Normal e Diabetic

1. Insulina etiquettate per iodo radio-active (I^{131}) dispare minus rapidemente ab le plasma de multe diabeticos que ab le plasma de subjectos de controlo normal o alteremente nondiabetic.
2. Es etiam a constatar un minus rapide degradation del etiquettate insulina in tal diabeticos que in le subjectos de controlo.
3. Il existe nulle apparente correlation inter iste observationes e le characteristicas clinic del diabeticos.
4. Studios in vitro supporta le these que "non-saturation" del componentes plasmatic con insulina es possibilemente responsabile in parte pro le apparente retention plasmatic de etiquettate insulina in vivo.

DISCUSSION

FRANCIS D. W. LUKENS, M.D., (*Philadelphia*): In view of the report by Drs. Milstein and Hausberger, would Dr. Williams and his co-workers consider adding the uptake of insulin by adipose tissue to his many other interesting measurements?

Secondly, have they ever tested insulin in normal subjects who have some allergy to insulin; that is, have they had a nondiabetic with allergy to insulin, and then seen what happened to this?

DR. WILLIAMS: No, we have not made such tests.

FREDERICK M. ALLEN, M.D., (*New York*): In regard to the distribution of insulin, it seems of interest to test large doses as being easiest to follow. I previously published experiments with injecting huge doses in the hind legs of animals (New England J. Med. *219*: 77, 1938; Ann. Int. Med. 12:1263 and 1870, 1939).

The effect is extreme depression and with sufficiently high doses (above 1,000 units for the strongly tolerant rat, several thousand units for rabbits, cats or dogs) the animal dies in spite of any glucose administration or any level of hyperglycemia. The hypoglycemia is not greatly different with small or large doses; for example, one rat receiving 20 units and another receiving 500 units may have their hypoglycemic convulsions at about two or two and a half hour intervals, and each recovers with a prompt injection of a fraction of a gram of glucose. But with the small insulin dose the animal acts well and there are only a few repetitions of the convulsions, whereas with the 500 units the depression is marked and the investigator must sit up for about forty-eight hours to combat the recurring hypoglycemia.

Since the depression persists in spite of hyperglycemia, it might hypothetically be attributed to a great excess of insulin throughout the body. But on cutting off the leg that received the insulin, the animal is quite promptly well. In other words, the greater part of the insulin is not diffused through the body but is lying unabsorbed in the leg. The marked toxicity can also be shown with the slowly absorbable protamine insulin.

As regards sugar distribution, years ago I gave a problem to Dr. Walter Palmer for comparison of blood and tissue sugars in diabetic and nondiabetic animals. The results can be found in his paper (J. Biol. Chem. 30:79, 1917). But I am specially interested today in observations which may throw light on something I published in 1913, namely the diuretic action of sugar. It is true that intravenous glucose can make polyuria by reason of hydremia; but hyperglycemia produced by any other mode of glucose administration in the normal animal fails to reproduce the diabetic polyuria. I speculated that a combined state of sugar in normal blood might explain the difference; but since that was disproved chemically it is now interesting to hear of a combination occurring in the cells. Thus, if free glucose enters into the kidney cells in the diabetic and not in the normal, the difference in diuresis may be explained.

THOMAS H. MCGAVACK, M.D., (*New York*): Have you any clinical evidence about differences between diabetics in which insulin was degraded at different rates?

DR. WILLIAMS, (*closing*): No, we could not find a correlation of the degree of degradation with such factors as severity of diabetes.

The Beneficial Effects of Cooking Food

Cooked foods are more digestible. The cooking of meat loosens the connective tissue so that it is more easily chewed and is of readier access to the gastric juices. Extreme heat, however, long continued, has an opposite effect. Another result of cooking is to render meat more attractive and appetizing, which in turn stimulates the digestive organs. Not only are vegetables made more appetizing by cooking, but, what is still more important, the starch cells under the influence of heat burst and permit the digestive juices to reach the contained starch. Breads and cakes are made light by cooking, for the contained gases expand and the water vaporizes to make the mass still lighter; while this is taking place, the albumins coagulate and "fix" the bread in this light state. The carbohydrate on the surface is partly caramelized, which gives the whole a more attractive appearance and flavor and thus renders it more digestible.

From the book *Nutrition and Diet in Health and Disease* by James S. McLester, M.D., and William J. Darby, M.D., Ph.D. Philadelphia, W. B. Saunders Co., 1952, 6th ed., pp. 141-44.

The Characteristics of a Satisfying Meal

The satiety values of the various foods show that a meal which contains meat gives the greatest degree of satisfaction, and if bread and potatoes are added, particularly the latter, the sense of comfort and well-being is increased. If the bread is buttered, so much the better; and if at the end of the meal something sweet is eaten, the satiety value becomes still greater. Thus is seen the rationale of that type of meal which the race has instinctively chosen: first, a soup (meat extractives); second, meat with potatoes, to which may be added certain other starchy vegetables; then a salad with oil dressing, and finally a dessert. This meal remains longest in the upper portion of the gastrointestinal tract, calls forth the greatest amount of secretory activity, and gives the greatest degree of satisfaction.

From the book *Nutrition and Diet in Health and Disease* by James S. McLester, M.D., and William J. Darby, M.D., Ph.D. Philadelphia, W. B. Saunders Co., 1952, 6th ed., p. 132.

Insulin Treatment of Juvenile Diabetes

Observations on the Combined Use of Intermediate and Regular Insulins

James A. McArthur, M.D., Salinas, California,*
and Robert L. Jackson, M.D.,† Columbia, Missouri

For many years the management of diabetes mellitus at the Pediatric Clinic of the State University of Iowa has had as its objective to attain and maintain physiologic control. To accomplish this end we have found the administration of insulin on a percentage distribution basis practicable.

Under the standard conditions of quantitative diet and exercise in the hospital, we obtained normoglycemic diurnal curves when four doses of regular insulin were distributed as 35, 22, 28, and 15 per cent of the total daily dosage, the injections being given one-half hour before meals and once during the night. This pattern of distribution, in keeping with the generally acceptable three-meal plan of the child, has guided us when modifying our regimen as new types of insulin have become available. We found it impossible to attain our objective using protamine-zinc insulin. In 1944, when globin insulin with zinc was made available, we started to use it in a regimen which we had developed in our clinic. In this plan, one dose of globin insulin with zinc given one hour before the evening meal replaced the evening and night doses of regular insulin.[1] In 1953, when NPH insulin was made available, we studied its use in place of globin insulin and observed no significant differences in the diurnal blood sugar curves for groups of well regulated diabetic children.[2]

The purpose of this study is to present the development of a satisfactory two-injection regimen employing mixtures of an intermediate insulin and regular insulin as the morning injection and an intermediate insulin as the evening injection. The intermediate insulins employed are NPH and globin insulin with zinc.

From the Department of Pediatrics, University of Missouri School of Medicine, Columbia, Missouri. The observations reported were made on patients under treatment at the State University of Iowa prior to Sept. 1, 1954.

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METHOD OF STUDY

Subjects used for the development of the new regimens were limited to diabetic children living under controlled conditions in the hospital. The nursing staff cooperated in an effort to attain accuracy in dosage of insulin, site and depth of injection, standardization of exercise, collection of urine specimens and recording of any variable factors which arose during the period of study. Competent dietitians were responsible for the calculation of diets and the weighing and preparation of food. All urine voided was analyzed by laboratory technicians, who also determined blood sugar values one or two days each week at the following hours: 7, 9, and 11 a.m., 4 and 10 p.m., and 2 and 6 a.m. All subjects used were emotionally adjusted and free from infections. Each child underwent a prolonged observation period during which the insulin requirement became constant for the standard condition imposed by the therapeutic regimen. All subjects remained free both from glycosuria and from clinically significant insulin reactions and maintained approximately normal diurnal blood sugar fluctuations.

Data for study of the regimen during hospitalization and under home conditions of the diabetic children have been compiled over a three-year period.

Our standard diet distribution during the control period was used for patients receiving regular insulin one-half hour before the morning and noon meals and globin insulin with zinc one hour before the evening meal. This diet distribution consists of 6/18 of the caloric intake at breakfast, 6/18 at noon, and 5/18 at supper, with an evening supplement of 1/18.

The type of diet distribution used by the experimental groups has been one in which the total diet for the day was also divided into 18 portions, with 4/18 being given at breakfast (7:15 a.m.), followed by a mid-morning snack approximately two to two and one-half hours after breakfast (9:30 a.m.) consisting of 2/18 of the total caloric intake for the day; the noon meal was 5/18 of the daily allowance, followed by a mid-afternoon snack at 3 p.m. of 1/18; supper at 4:45 p.m. was 5/18, and an evening snack at 9 p.m., 1/18. This

diet distribution was adjusted to meet the varying needs of patients under home management.

IN-PATIENTS

A total of 16 patients was observed during hospitalization. As an initial program, separate injections of an intermediate insulin and regular insulin were given in the morning, the third injection of the day being an intermediate insulin administered in the evening.

Various proportions of the regular and intermediate insulins were studied beginning with a percentage distribution of the twenty-four-hour insulin requirement of 30 per cent NPH or globin and 30 per cent regular insulin in the morning, and the remaining 40 per cent as NPH or globin in the evening. We shall designate this distribution for convenience as the 30-30-40 distribution, the intermediate insulin being the first and last named in the series. We progressed through the percentage distributions 35-25-40, 40-25-35, and 45-20-35 until the most satisfactory distribution of 50-15-35 was reached. It will be noted that the percentage of intermediate insulin in the morning injections was gradually increased, whereas the percentage of regular insulin was gradually decreased. The percentage of the total daily quantity of insulin given as an intermediate insulin in the evening was progressively decreased.

To ascertain the effect of the varying proportions of regular and intermediate insulin on the diurnal blood sugar values, each type of distribution was analyzed and compared with the range of diurnal blood sugar values obtained in six nondiabetic children and also the mean and range of values observed in 55 hospitalized diabetic children in excellent control. Figure 1 is based on 12 diurnal blood sugar curves of two patients using the 30-30-40 insulin distribution. It was observed that there was an initial fall in the blood sugar level to the lowest levels at 9 a.m., followed by a rise to peak levels at 4 p.m., with subsequent gradual decline in blood sugar levels until the 2 a.m. specimen, and then a slight increase in the 6 a.m. specimen.

Figure 2 is based on three diurnal blood sugar curves of two patients using the 35-25-40 distribution of insulin. The lowest levels occurred in the 11 a.m. specimens, and the high levels again were observed at 4 p.m. The peak was followed by a steady decline in blood sugar levels until the 2 a.m. specimen, and then a rise during the 6 a.m. tests.

Figure 3 shows the average of two diurnals of a patient receiving insulin distributed in the 40-25-35 plan. The lowest blood sugar values of any distribution test were noted in this plan. Low levels were observed at

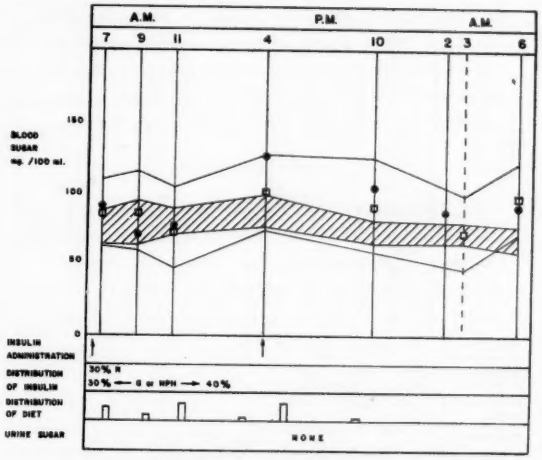

FIG. 1. The cross-hatched area represents the range of 12 diurnal blood sugar values observed in 6 nondiabetic children. The open squares and the area between the two black lines represent the mean and mean plus and minus one standard deviation, respectively, of 176 diurnal blood sugar values observed in 55 hospitalized diabetic children in excellent control. The solid dots represent the mean of 12 diurnal blood sugar values of 2 patients receiving separate injections of regular and an intermediate insulin in the morning and an injection of an intermediate insulin in the evening. The percentage distribution of the insulin is 30-30-40.

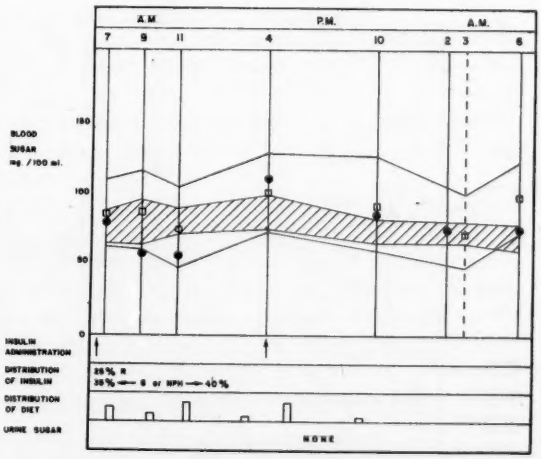

FIG. 2. The cross-hatched area, the area between the black lines, and the open squares represent the same as in figure 1. The solid dots represent the mean of three diurnal blood sugar values of two patients receiving separate injections of regular and an intermediate insulin in the morning and an injection of an intermediate insulin in the evening. The percentage distribution of the insulin is 35-25-40.

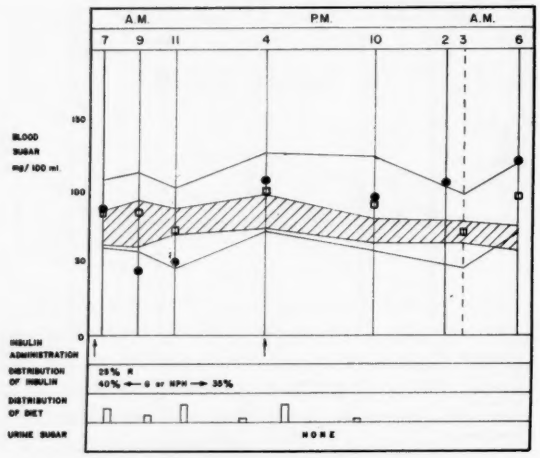

FIG. 3. The cross-hatched area, the area between the black lines, and the open squares represent the same as in figure 1. The solid dots represent the mean of two diurnal blood sugar values of one patient receiving separate injections of regular and an intermediate insulin in the morning and an injection of an intermediate insulin in the evening. The percentage distribution of the insulin is 40-25-35.

9 a.m., with a peak at 4 p.m., followed by a decline until 10 p.m., and then a rise at 2 and 6 a.m.

Figure 4, based on three diurnal blood sugar curves of one patient using the 45-20-35 distribution, shows the highest peak levels, which were reached at 4 and 10 p.m.,

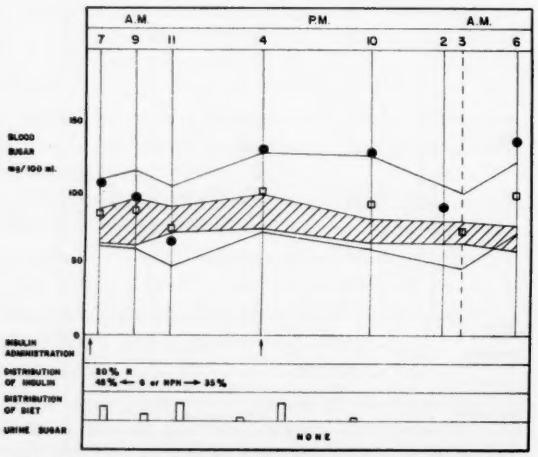

FIG. 4. The cross-hatched area, the area between the black lines, and the open squares represent the same as in figure 1. The solid dots represent the mean of three diurnal blood sugar values of one patient receiving separate injections of regular and an intermediate insulin in the morning and an injection of an intermediate insulin in the evening. The percentage distribution of the insulin is 45-20-35.

following an initial drop to the lowest level at 11 a.m. Again there was a decline from peak level until the 2 a.m. tests, with subsequent rise in the 6 a.m. specimens.

Figure 5 shows the mean of 18 diurnal blood sugar values of four patients receiving insulin distributed according to the 50-15-35 plan. This distribution resulted in the most consistent average blood sugar level, with a gradual decline from 7 to 11 a.m., followed by increasing values until the peak was reached at 10 p.m., with a slight decrease at 2 a.m. and a minimal rise at 6 a.m.

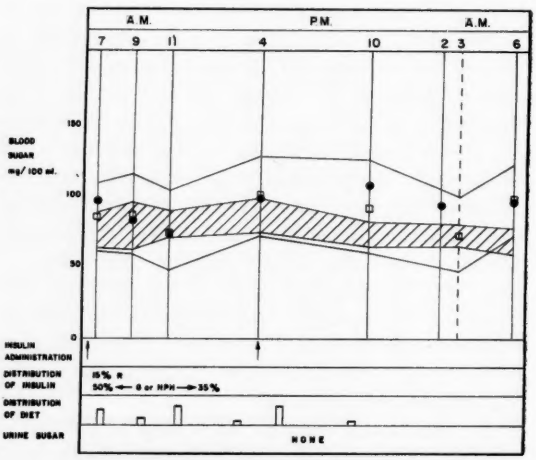

FIG. 5. The cross-hatched area, the area between the black lines, and the open squares represent the same as in figure 1. The solid dots represent the mean of 18 diurnal blood sugar values of four patients receiving separate injections of regular and an intermediate insulin in the morning and an injection of an intermediate insulin in the evening. The percentage distribution of the insulin is 50-15-35.

The next step was an attempt to use a two-injection program: a mixture of intermediate and regular insulin administered as a single injection before breakfast, and an injection of intermediate insulin in the evening. On the basis of our studies with separate injections, the 50-15-35 distribution was selected and a trial was made of a mixture of NPH and regular insulin as the morning injection and NPH for the evening. Figure 6 depicts the mean of nine diurnal blood sugar curves of three patients using this plan. The diurnal blood sugar values are not as smooth as those obtained by separate injections, which may indicate a certain amount of interaction between NPH and regular insulin when mixed. The blood sugar values, however, indicate adequate control, remaining within one standard deviation of the mean values of diabetic children in ideal control.

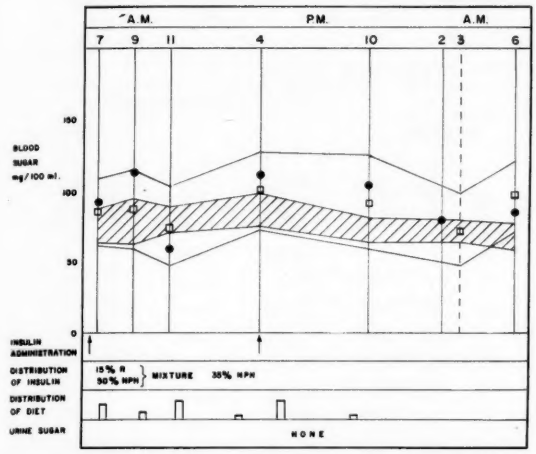

FIG. 6. The cross-hatched area, the area between the black lines, and the open squares represent the same as in figure 1. The solid dots represent the mean of nine diurnal blood sugar values of three patients receiving a mixture of NPH and regular insulin in the morning and an injection of NPH insulin in the evening. The percentage distribution of the insulin is 50-15-35.

Trials of a program using a mixture of globin and regular insulin as the morning injection and globin for the evening were made. On the basis of the separate injection plans and the apparent loose combination between globin and insulin in which the relative proportions of the two ingredients may vary over a wide range, the percentage distribution 45-20-35 was selected. Figure 7 shows the mean of seven diurnal blood sugar curves of three patients using the mixture program with the 45-20-35 percentage distribution. The blood sugar values using this distribution indicated an even and adequate control.

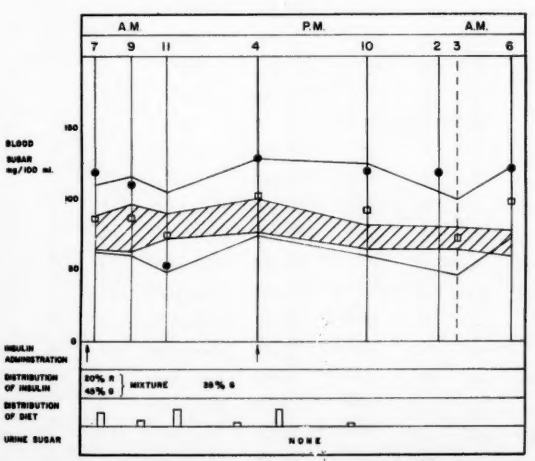

FIG. 7. The cross-hatched area, the area between the black lines, and the open squares represent the same as in figure 1. The solid dots represent the mean of seven diurnal blood sugar values of three patients receiving a mixture of globin insulin with zinc and regular in the morning and an injection of globin insulin in the evening. The percentage distribution of the insulin is 45-20-35.

OUT-PATIENTS

After we had demonstrated to our satisfaction that diabetic children could be well controlled as in-patients with a mixture of regular and intermediate insulin, we began studies on this program on an out-patient basis in an attempt to determine whether or not it would prove to be a practical method of home regulation of juvenile diabetics. Only a few trials of the globin and regular mixture have been made under home conditions.

Of the 80 patients who have received the NPH mixture on an out-patient basis, 39 have records which are deemed reliable and complete enough for research studies. Table 1 is a summary of some of our findings in this group of patients.

The 39 children selected for this study have been arranged according to their degree of control during the experimental period (regimen of NPH and regular insulin mixture). Each subject has been observed for an equal length of time during the control period and during the study of NPH and regular mixture; and, in all but a few cases, the two periods have been contiguous, representing a total of 2616 patient weeks for the entire study, or 1308 patient weeks of observation of the regimen of NPH and regular insulin mixture.

It was noted that there was no dramatic change in the level of diabetic control in most cases when a patient was changed from the control regimen to the program of NPH and regular insulin mixture. In some instances diabetic control improved, while in others it was less satisfactory.

The number of insulin reactions also was not appreciably affected by a change in regimen but, as should be expected, reactions were more frequent in those patients in suboptimal diabetic control. Six patients in the study had ten or more insulin reactions during one or the other of the observation periods. Electroencephalographic studies were available in five of these cases with normal findings in three, borderline in one, and abnormal in one.

DISCUSSION

When the NPH and regular insulin mixture is used for control of a juvenile diabetic in the home, it has been our policy to ascertain first the degree of proficiency with which the parents are able to manage the problem using the standard regimen; that is, regular insulin before the morning and noon meals and globin or NPH

TABLE 1

No.	Sex	Chronologic age years and months: At onset of diabetes mellitus	When disease completely controlled	At beginning of study	Length of each observation period (weeks)	Observation Periods: Control: Range of insulin dosage (units)	Degree of control	Reactions: Mild	Moderate	Severe	Experimental: Range of insulin dosage (units)	Level of control	Reactions: Mild	Moderate	Severe
1	F	5-4	5-6	6-0	20	7-15	Good	0	0	0	15-20	Good	3	0	0
2	F	5-0	5-1	7-3	32	17-24	Good	0	1	0	24-32	Good	4	0	0
3	M	10-6	10-7	10-9	12	10-42	Fair	0	0	0	24-35	Good	0	0	0
4	M	11-1	11-2	11-2	36	25-33	Good	1	0	0	31-51	Good	1	0	0
5	F	1-5	1-7	11-4	28	49-53	Fair-poor	0	0	0	51-54	Good	0	0	0
6	M	6-2	6-4	12-5	52	48-66	Good	4	1	0	66-73	Good	6	0	0
7	M	12-2	12-3	12-10	52	45-57	Good	0	0	0	57-90	Good	0	0	0
8	F	2-5	2-7	13-5	16	80-104	Good	0	0	0	64-104	Good	0	0	0
9	M	10-4	10-5	13-6	24	60-84	Good	0	0	0	71-85	Good	0	0	0
10	M	13-11	14-1	14-1	32	54-64	Good	0	0	0	54-88	Good	0	0	0
11	F	8-11	9-0	14-2	12	70-101	Good	0	0	0	72-51	Good	0	0	0
12	M	7-8	7-10	14-5	32	69-120	Good	0	0	0	116-128	Good	0	0	0
13	M	14-2	14-4	14-7	52	9-14	Good	0	0	0	13-14	Good	1	0	0
14	F	9-6	9-7	14-10	32	38-42	Good	0	0	0	38-39	Good	0	0	0
15	M	13-10	14-0	14-10	40	48-73	Good	0	0	0	51-75	Good	0	0	0
16	M	15-1	15-3	15-7	8	30-31	Good	1	0	0	38-40	Good	3	0	0
17	F	16-0	16-3	16-8	52	48-60	Good	2	0	0	52-57	Good	2	0	0
18	M	14-10	15-0	18-1	24	35-38	Good	0	0	0	35-38	Good	0	0	0
19	M	2-10	2-11	3-9	52	10-13	Fair	2	0	0	11-12	Fair	0	0	0
20	M	5-2	5-3	5-3	36	8-14	Good	0	0	0	10-18	Fair	1	0	0
21	F	4-5	4-6	5-1	12	9-13	Fair	1	0	0	9-18	Fair	0	0	0
22	F	4-6	4-8	6-5	16	21-25	Fair-poor	5	1	0	23-26	Fair	2	2	0
23	M	3-10	4-0	7-7	52	17-25	Fair	10	0	0	30-40	Fair	15	4	0
24	M	0-9	0-11	11-9	40	30-42	Good	2	0	0	55-84	Fair	4	0	0
25	M	2-3	2-5	13-11	28	61-72	Fair	4	0	0	68-108	Fair	10	1	0
26	F	3-1	3-4	17-6	36	51-77	Fair	22	1	0	51	Fair	0	0	0
27	F	6-2	6-4	17-7	12	76-80	Fair-poor	0	0	0	80-81	Fair	0	0	0
28	F	10-3	10-7	18-2	48	49-57	Fair	4	2	0	54-60	Fair	1	0	1
29	F	3-0	3-5	4-10	8	23-32	Fair-poor	4	0	0	28-39	Fair-poor	1	0	0
30	M	4-9	5-1	5-3	48	11-27	Fair-poor	0	0	0	30-34	Fair-poor	0	0	0
31	F	4-6	4-10	5-4	64	10-30	Fair-poor	4	3	0	28-40	Fair-poor	10	0	1
32	F	4-8	5-0	7-6	28	39-49	Fair-poor	20	0	0	32-48	Fair-poor	10	0	0
33	F	5-5	5-6	10-0	24	25-42	Fair-poor	4	0	0	42-51	Fair-poor	0	0	0
34	M	8-8	8-10	10-1	44	41-47	Fair	0	0	0	42-53	Fair-poor	1	0	0
35	M	8-1	8-2	12-10	12	36-38	Fair-poor	0	0	0	36-39	Fair-poor	1	0	0
36	M	5-7	5-9	13-0	24	49-60	Fair	0	0	0	51-60	Fair-poor	0	0	0
37	F	7-4	7-5	14-1	8	68-75	Fair-poor	15	0	0	58-92	Fair-poor	19	0	0
38	M	11-2	11-3	16-6	16	90-95	Fair-poor	0	0	0	88-97	Fair-poor	1	0	0
39	F	1-6	1-8	17-9	32	56-68	Fair-poor	0	0	0	49-60	Fair-poor	0	0	0

*Basic diet prescribed permits fluctuations in caloric intake to compensate for variations in physical activity.

Basic diet*	
Control period	Experimental period
No change	Increased 200 cal.
No change	Increased 200 cal.
No change	No change
Increased 200 cal.	Increased 200 cal. more
No change	Increased 200 cal.
No change	Increased 400 cal.
No change	Increased 400 cal.
No change	Decreased 200 cal.
No change	No change
Decreased 200 cal.	Increased 300 cal.
No change	No change
No change	No change
No change	No change
No change	Decreased 200 cal.
No change	No change
No change	Increased 300 cal.
Decreased 200 cal.	No change
No change	Increased 200 cal.
No change	Increased 200 cal.
Increased 400 cal.	Increased 200 cal. more
No change	Increased 200 cal.
No change	No change
Increased 400 cal.	Increased 200 cal. more
Increased 200 cal.	No change
Increased 300 cal.	Increased 400 cal. more
Decreased 400 cal.	No change
No change	No change
Decreased 200 cal.	No change
No change	No change
Increased 200 cal.	Increased 400 cal. more
Increased 200 cal.	Decreased 200 cal.
No change	No change
No change	No change
No change	No change
No change	No change
No change	No change
No change	Decreased 200 cal.
No change	Increased 150 cal.
No change	Increased 200 cal.

before the evening meal as described in previous papers.[1, 2] This policy serves a dual purpose. First, it is thought that parents unable to control a child satisfactorily by using this program will, in general, not be able to maintain adequate control with a modified regimen. Second, it is desirable that the parents be familiar with the method of control using regular insulin, so that in the event of intercurrent infection or danger of wide and sudden fluctuations in insulin requirements, they will be able to use a program utilizing insulin with a shorter duration of action to maintain better control when the insulin dosage is changing rapidly.

During hospitalization, we have been able without exception thus far to maintain good diabetic control in patients by using the NPH or globin and regular insulin mixture. On an out-patient basis, however, a small percentage of patients have been changed back to two doses of regular and one of intermediate insulin, the most common reason given being inability to control the glycosuria as well when using the new program.

Other difficulties reported by a few patients relate to the problem of the mid-morning and mid-afternoon snacks. In some instances the proper type of food is not readily available so that a lunch basket must be carried to school. This problem is most evident in children of grade school age; in the older age groups the mid-morning and mid-afternoon supplements fit very conveniently into the recess periods when other children also are eating snacks.

Another factor entering into the picture in some patients who have reverted to the previous regimen is that of great confidence in the standard program, such that it is difficult for the parents to comprehend how any other program could be as satisfactory. At the first hint of difficulty they return to the program with which they are most familiar and in which their confidence lies.

On the other hand, the vast majority of patients after changing to the program of NPH and regular insulin mixture are extremely enthusiastic. Greatly appreciated is the elimination of the noon insulin injection. Others express gratitude for being able to participate in the snacks with a clear conscience, enhancing their feeling of normality and boosting their morale. It was observed, however, that in some instances patients overstepped their new-found freedom.

It has been our experience that in some patients who had been extremely difficult to control using other programs, good control has followed institution of the new regimen.

At the present time a total of 81 patients have used the NPH-regular mixture with six reversions to the older program.

Studies in progress at this time indicate that satisfactory control may also be maintained using a two-injection schedule consisting of a globin-regular mixture in the morning and an injection of globin insulin in the evening. The dietary distribution is the same as that used in the NPH-regular mixture program.

SUMMARY

A program of juvenile diabetic management using a mixture of NPH and regular insulin as the morning injection and NPH for the evening injection is presented. Also discussed are the studies leading to the selection of a satisfactory ratio for the mixture and the type of dietary distribution. Studies of similar regimens using a mixture of globin and regular insulin as the morning injection and globin insulin for the evening injection resulted in satisfactory control of hospitalized patients. Further studies with globin and regular insulin mixture are in progress.

Follow-up statistics on those patients using the new program at home are tabulated.

It is now possible to maintain satisfactory regulation of juvenile diabetes in approximately 90 per cent of cases, using a two-injection program, a mixture of NPH or globin and regular insulin in the morning and globin or NPH insulin in the evening.

SUMMARIO IN INTERLINGUA

Insulina in le Tractamento de Diabeticos Juvenil: Observationes Super le Uso Combinate de Insulinas Intermediari e Regular

Es presentate un programma therapeutic pro diabeticos juvenil, usante un mixtura de insulina NPH e insulina regular como injection matinal e insulina NPH como injection vespertin. Es etiam discutite le studios que establiva un satisfacente proportion del insulinas in le mixtura e un recommendabile typo de distribution dietari. Studios con un simile programma usante un mixtura de insulina globinic e insulina regular como injection matinal e insulina globinic como injection vespertin resultava in satisfacente controlo de patientes hospitalisate. Studios additional con insulinas globinic e regular es in execution.

Es presentate tabulationes statistic post-hospitalari pro le patientes qui usa le nove programma a lor domicilios.

Il es nunc possibile mantener un satisfacente regulation in circa 90 pro cento del casos de diabete juvenil, usante un programma a duo injectiones: un mixtura de insulina NPH o insulina globinic con insulina regular in le matino e insulina NPH o insulina globinic al vespere.

ACKNOWLEDGMENT

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Steatorrhea Complicating Diabetes Mellitus with Neuropathy

Report of Cases without Apparent External Pancreatic Insufficiency

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Disturbances of gastrointestinal function have frequently been observed in association with diabetes mellitus. The disorders which have been reported include gastric atony and dilatation, postprandial abdominal cramping, severe constipation, and intractable diarrhea characterized by watery stools, nocturnal exacerbations and fecal incontinence.[2, 10, 14, 15, 17-20] These disturbances have been attributed by many investigators to alterations in gastrointestinal motility secondary to visceral diabetic neuropathy. The purpose of the present report is to call attention to a group of patients with diabetes mellitus and neuropathy who exhibited diarrhea and steatorrhea which apparently could not be attributed to external pancreatic insufficiency.

REPORT OF CASES

Case 1. A white woman, aged 31 years, was first seen at the Mayo Clinic in 1951 because of diabetes mellitus of 17 years' duration. There was a family history of diabetes. Control of the patient's diabetes had been poor. No history of gastrointestinal symptoms was elicited. The patient was dismissed with instructions to follow a program of diet and insulin.

The patient returned in 1953 because of frequent insulin reactions. Symptoms of gaseous abdominal distention and diarrhea without nocturnal fecal incontinence had been noted for the preceding four months. There had been no loss of weight and no pain suggestive of pancreatitis.

On examination the blood pressure was 104 mm. of mercury systolic and 70 diastolic. There was no postural hypotension. The ocular fundi were normal. The results of examination of the abdomen were negative. With the exception of the absence of sweating below the level of the thorax in response to heat (figure 1) the results of neurologic examination were normal. The laboratory findings are given in tables 1 and 2.

Because of the steatorrhea the patient was advised to follow a diet limited in fat to 30 gm. daily. Subsequent correspondence indicated that only a temporary remission of symptoms was noted with the initiation of this diet. Subsequent diarrhea was not improved by therapy with pancreatin.

Case 2. A white man, aged 34 years, was seen at the clinic in 1954 with a history of diabetes mellitus of 14 years' duration. The family history was positive for diabetes. Control of the patient's diabetes had been poor, as evidenced by a lack of dietary regulation and a history of frequent insulin reactions. For six years the patient had had diarrhea with four to eight foamy, greasy stools daily. Nocturnal diarrhea and fecal incontinence were distressing symptoms, and the patient experienced exacerbations of the diarrhea following meals. For five years, impotence had been present. Four years prior to examination subtotal gastrectomy had been done because of a bleeding duodenal ulcer. Postural dizziness had been present for five months. The patient also noted nocturnal paresthesias and shooting pains in his legs. There had been a loss of 20 pounds in the 10 years prior to examination at the clinic. There had been no pain suggestive of pancreatitis.

On examination, the blood pressure was 120 mm. of mercury systolic and 90 diastolic; after the patient stood for 5 minutes, this decreased to 74 mm. systolic and 60 diastolic and the patient felt dizzy. The pupillary reactions and ocular fundi were normal. The results of examination of the abdomen were unremarkable. The tone of the anal sphincter was decreased. Muscle stretch reflexes were absent in the legs and hypoactive in the arms. Vibratory sense was absent in the toes. The sweating pattern is shown in figure 1. The laboratory data are included in tables 1 and 2. During a brief period of observation, a low dietary intake of fat was associated with improvement in

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the gastrointestinal symptoms.

Case 3. A white man, aged 35 years, came to the clinic in 1952 with a history of diabetes mellitus of 5 years' duration. There was no family history of diabetes. Careful control of the diabetes had not been attempted, as indicated by the lack of frequent urine testing for sugar. For 3 years the patient had been impotent and had suffered from diarrhea characterized by the passage of 10 to 12 stools per 24-hour period. The patient noted postprandial exacerbations of diarrhea, with the appearance in the stool of food ingested as recently as 15 minutes previously. Although he passed the majority of his stools during the daytime, he also had nocturnal diarrhea associated with fecal incontinence at least once nightly. There were no gross steatorrhea and no history of pain suggestive of pancreatitis. The patient had lost 44 pounds since the onset of diarrhea.

On examination, the blood pressure varied between 90 and 110 mm. of mercury systolic and between 50 and 60 diastolic when the patient was supine and measured 70 mm. systolic and 56 diastolic with the patient standing. The pupillary reactions and ocular fundi were normal. There were no abnormalities on abdominal examination. The knee jerks and ankle jerks were absent and vibratory sensation was impaired at the ankles. Slight weakness of the muscles of the pelvic girdle and of the anterior and posterior tibial muscle groups was noted. There was no sweating below the waist in response to heating (figure 1). The laboratory findings are listed in tables 1 and 2. Therapeutic trials of large doses of pancreatin, banthine, biohepulin, and cortisone provided no symptomatic benefit with respect to the diarrhea.

Case 4. A white man, aged 31 years, first came to the clinic in 1946 with a history of diabetes mellitus of 10 years' duration. There was a family history of diabetes. Control of the diabetes had been poor in that he had experienced numerous insulin reactions and an episode of coma. For four years the patient had noted diarrhea; this was intermittent initially but had been constant for three years. There were as many as 18 stools during the day and 5 stools during the night, at which time fecal incontinence was frequently present. The stools appeared greasy, floated on water and often contained particles of food that had been ingested as recently as three hours previously. There were no history of abdominal pain and no loss of weight. The patient had been impotent for two years.

On examination the blood pressure was 98 mm. of mercury systolic and 78 diastolic while the patient was supine. These levels fell to 56 mm. systolic and 40 diastolic with the patient standing. The pupils were of the Argyll-Robertson type; the ocular fundi exhibited diabetic retinopathy. The results of examination of the abdomen were unremarkable. The knee jerks were diminished and the ankle jerks absent. Pain and temperature perception was diminished in patchy areas over the entire body. No sweating test was done. Laboratory data are included in table 1. Quantitative studies of fat excretion were not carried out. Therapy with 5 cc. of crude liver extract daily for 10 days provided no improvement of the diarrhea, and further similar treatment following the patient's return home was also ineffective.

Because of persistent, incapacitating diarrhea the patient returned in 1947. Fecal fat and nitrogen during control periods and during periods of therapy with pancreatin while the dietary fat was 100 gm. daily are given in table 3. It is apparent that during therapy the steatorrhea was more severe than during the control periods. All attempts to control the gastrointestinal symptoms were unsuccessful, and correspondence indicated that severe diarrhea persisted until the patient's death in 1948.

Case 5. A white man, aged 36 years, was first seen at the clinic in 1934 with a history of diabetes mellitus of two years'

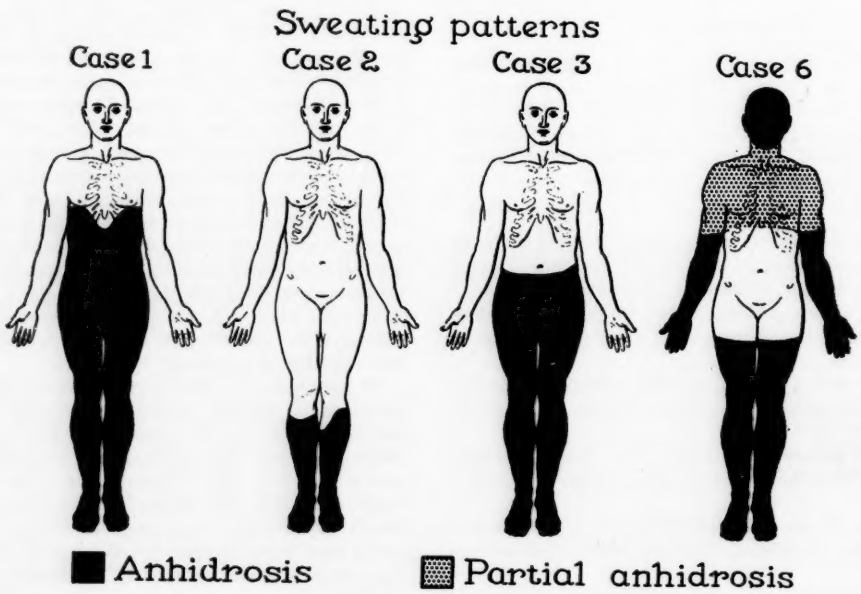

FIG. 1 Sweating patterns in four cases.

TABLE 1

Steatorrhea complicating diabetes mellitus with neuropathy: laboratory data in six cases*

Determination	Case 1	2†	3†	4†	5†	6† 1942	6† 1945
Albuminuria (grade, basis 4)	0	0	1	1	1	0	2
Hemoglobin (gm. per 100 cc.)	12.6	11.6	11.7	13.8	9.3	11.7	12.4
Erythrocytes (million per cu. mm.)	4.45	4.60	4.91	4.31	3.03	4.17	4.31
Blood sugar (mg. per 100 cc.)	440	260	390	208	470	248	63
Macrocytosis	–	–	0	0	0	0	+
Serum protein (gm. per 100 cc.)	5.25	–	5.25	6.80	5.90	4.70	6.20
Albumin-globulin ratio	1.43:1	–	0.86:1	1.44:1	1.82:1	1.58:1	1.80:1
Sulfobromophthalein dye retention (% in 1 hr.)	–	–	–	0	0	0	–
Prothrombin time (normal 19 sec.)	–	–	19	17	20	19	–
Serum calcium (mg. per 100 cc.)	–	9.6	8.8	9.9	9.3	9.5	9.8
Serum phosphate (mg. per 100 cc.)	–	–	3.2	3.9	3.3	–	3.2
Blood urea (mg. per 100 cc.)	–	32	14	–	66	36	50
Serum amylase (normal <320 units)	8.0	–	–	106	160	106	–
Serum lipase (normal <0.3 cc. N/10 base)	0.1	–	–	0.3	0.3	0.0	–
Roentgenographic studies:							
Pancreatic calcification	0	–	0	–	0	0	0
Stomach	–	0	0	atonic	0	0	Retention
Small intestine	Deficiency pattern	0	Deficiency pattern	0	0	0	0
Colon	0	0	0	0	0	–	–
Gastric acidity (units: free/total)	–	–	–	46/60	60/80	38/48	20/34
Cerebrospinal-fluid protein (mg./100 cc.)	–	–	–	60‡	30‡	40‡	–

\+ indicates finding present.
0 indicates normal finding.
– indicates no data.

* Kline test for syphilis negative in all cases.
† Proctoscopic examination negative.
‡ Gold sol and serology negative.

TABLE 2

Data on intake and excretion of fat

Case	Dietary fat, gm. per day	Fecal fat: Gm. per day	Fecal fat: Per cent of dry weight of stool
1	104	69.5	63.3
2	145	66.7	46.5
3	122	51.0	48.0
4	100	24.9	27.5
5	100	40.7	45.4
6	96	13.9	—
Normal	100	<7.5	<30

duration. The family history was positive for diabetes. For two years he had noted an epigastric burning pain with relief on ingestion of food, and for three months he had noted constipation. Examination of the eyes revealed diabetic retinopathy; the pupillary reflexes were normal. The physical examination disclosed no other abnormalities. A duodenal ulcer was demon-

TABLE 3

Fecal excretion of fat and nitrogen
Effect of pancreatin*

Case	Dietary fat, gm. per day	Therapy	Duration, days	Gm. per day: Fecal fat	Gm. per day: Fecal nitrogen
4	100		3	24.9	4.76
		Pancreatin, 5 gm. t.i.d.	3	30.3	6.37
			3	23.8	7.16
5	100		3	40.7	5.20
		Pancreatin, 5 gm. t.i.d.	3	47.9	5.53
			3	39.2	3.83
6	96 (1942)		15	12.1	4.30
		Pancreatin, 10 gm. t.i.d.	10	24.4	5.95
			5	19.6	4.4
		Pancreatin, 6.7 gm. t.i.d.	10	25.6	6.25
			5	13.3	3.9
	100 (1945)		6	18.6	4.7

*Triple-strength, enteric-coated tablets (0.3 gm. each).

strated roentgenographically. The patient was placed on a program of medical treatment for diabetes and duodenal ulcer. He returned to the clinic three months later because of continuous pain in his feet, alternating constipation and diarrhea, and epigastric distress which was not characteristic of either ulcer or pancreatic pain. Neurologic examination disclosed only diminished muscle stretch reflexes and vibratory perception in the legs.

The patient returned to the clinic in 1944 because of intermittent, severe diarrhea of 10 years' duration characterized by the appearance of food particles in the stools as early as 2 hours after meals and by nocturnal fecal incontinence. The patient stated he had had as many as 50 bowel movements in a 24-hour period. There was no gross steatorrhea. The patient had lost 9 pounds during the preceding 10 years. He had noted paresthesias of the feet for four years.

On examination the blood pressure was 115 mm. of mercury systolic and 50 diastolic. The pupils were Argyll-Robertson in type. Diabetic retinopathy was again noted. The liver was palpable two fingerbreadths below the right costal margin. The tone of the anal sphincter was diminished. Knee and ankle jerks were absent and the perception of pain, light touch and vibration was impaired in the lower extremities. There was minimal edema of the ankles. Three hundred cubic centimeters of residual urine were found in the bladder immediately after urination. Laboratory findings are given in tables 1, 2 and 3.

Attempts to study the duodenal contents following administration of secretin were unsuccessful because the tube failed to enter the duodenum. The results of studies carried out while the dietary intake of fat was 100 gm. per day, given in table 3, indicated that the patient had marked steatorrhea and azotorrhea, which were intensified during therapy with pancreatin. Following the patient's return home, severe diarrhea persisted in spite of all therapeutic attempts, including further oral treatment with pancreatin. The patient died in 1946.

Case 6. A white man, aged 35 years, was first seen at the clinic in 1942. At that time there were a history of severe diabetes mellitus of 12 years' duration and a positive family history for diabetes. For the preceding 6 years the patient had noted intermittent diarrhea with as many as 20 stools daily. Food particles were frequently noted in the stools following meals; the patient also experienced nocturnal diarrhea with fecal incontinence. There was no history of pain suggestive of pancreatitis. For four years the patient had been impotent. For one year he had noted paresthesias involving the feet. During the four weeks immediately preceding exemination there had been difficulty in urinating. The patient had lost 20 pounds in the 6-month period prior to his coming to the clinic.

On examination while the patient was supine, the blood pressure was 120 mm. of mercury systolic and 80 diastolic and the pulse rate was 80 beats per minute. After the patient had stood for 5 minutes, the blood pressure was 70 mm. systolic and 50 diastolic and the pulse rate was 92. The pupils reacted poorly to both light and accommodation. Diabetic retinopathy was present. There was no glossitis. The results of examination of the abdomen were negative. The tone of the anal sphincter was diminished. The knee and ankle jerks were absent, and vibratory perception was diminished at the ankles. The sweating pattern is shown in figure 1. Neurogenic vesical dysfunction was evident on a cystometrogram. The entire neurologic syndrome was characteristic of pseudotabes diabetica. The results of laboratory studies are given in tables 1, 2, and 3. The patient noted a definite increase in the severity of his diarrhea and abdominal discomfort during the time he was taking pancreatin.

A transurethral resection of the vesical neck was done for control of urinary retention. Following the patient's return home, therapy with liver extract and thiamine was instituted. Intermittent diarrhea with three to five watery stools daily continued although other symptoms of neuritis became quiescent. Further trials of treatment with pancreatin were of no benefit.

The patient returned to the clinic in 1945 because of a protracted episode of malaise, anorexia, and vomiting following a respiratory infection six weeks previously. There had been a loss of 23 pounds during the preceding 4 months. The findings on physical examination were similar to those noted in 1942 except that the liver was palpable one fingerbreadth below the right costal margin. Laboratory findings at this visit are given in tables 1 and 3.

The patient died three months after his return home, a few hours after the onset of upper abdominal pain. At necropsy elsewhere the pancreas weighed 135 gm. and gross evidence of destruction or atrophy was lacking. On histologic study the acini were of usual appearance, although in some areas there was an increase of interlobular connective tissue. The stomach and small intestine were markedly distended but otherwise grossly normal. Other findings were myocardial fibrosis, acute pyelonephritis with minute abscesses of the kidneys, pulmonary congestion, cloudy swelling of the liver, and fibrosis of the spleen.

COMMENT

The symptoms of intractable diarrhea with postprandial and nocturnal exacerbations and fecal incontinence in the foregoing cases (table 4) are similar to those previously reported in cases of diabetic diarrhea in which steatorrhea had not been demonstrated. It should be noted that the diabetes antedated the onset of gastrointestinal symptoms by an average of seven years and a minimal interval of two years. The diabetes was severe in all cases, requiring more than 30 units of insulin daily for control (table 5). Three of the six patients had diabetic retinopathy, and in two there was evidence of nephropathy with renal insufficiency. In all cases there were neurologic abnormalities, which are presented in table 6. The finding of altered sweating patterns (figure 1), postural hypotension, impotence, vesical dysfunction, and pupillary abnormalities provided evidence of widespread autonomic neuropathy, which has previously been reported in association with diabetes mellitus.[6, 9, 11, 16–18, 20, 21]

Although there was no history of bulky, malodorous stools, the laboratory evidence of steatorrhea was striking in all cases (table 2). In addition three cases, in which nitrogen balance studies were performed, exhibited an associated azotorrhea. In all instances the gastrointestinal symptoms were exceedingly disturbing to the

TABLE 4

Steatorrhea complicating diabetes mellitus with neuropathy
Characteristics of the diarrhea in six cases

	Cases
Nocturnal occurrence	5
Fecal incontinence	5
Postprandial exacerbation	5
Associated abdominal cramping	3

TABLE 5

Steatorrhea complicating diabetes mellitus with neuropathy
Clinical data in six cases

		Duration, years	
Case*	Age (years) and sex	Diabetes prior to diarrhea	Diarrhea
1	31F	19	4/12
2	34M	8	6
3	35M	2	3
4	31M	6	5
5	36M	2	10
6	35M	6	9
Average	33.7	7.0	5.5

*Diabetes, grade 4, was present in all cases. Grade 4 indicates that more than 30 units of insulin are required daily.

TABLE 6

Neurologic abnormalities in six cases

Symptom or finding	Cases
Fecal incontinence	5
Ankle jerks absent	5
Abnormal sweating pattern (data in 4 cases)	4
Impotence (data on 4 males)	4
Sensory disturbance	4
Abnormal response of pupils	3
Postural hypotension	2
Vesical dysfunction	2
Neuritic pains	2

patients. Attempts to alleviate the diarrhea by treatment with pancreatin, banthine, atropine, vitamins, cortisone, and parenteral liver extract were unsuccessful. In addition, intake-excretion studies of three patients during periods of treatment with pancreatin revealed an increase rather than a decrease in the degree of steatorrhea and azotorrhea (table 3).

A search for the basis of the gastrointestinal symptoms and the steatorrhea was made in all cases. Coexisting diabetes and steatorrhea due to involvement of the pancreas by chronic pancreatitis or neoplasm were strongly considered in the differential diagnosis. However, the clinical picture was not that usually associated with destructive or obstructive lesions involving the acinar tissue of the pancreas, and in no case was it possible to establish the presence of external pancreatic insufficiency. The lack of response to treatment with large doses of a preparation of pancreatin that has uniformly given satisfactory results in the control of steatorrhea in patients with known external pancreatic insufficiency constitutes strong evidence against pancreatic steatorrhea. Furthermore, in the one case in which necropsy findings are available there was no postmortem evidence of destruction or obstruction of the pancreatic acini. Attempts in four cases to study the duodenal contents after stimulation of the external secretion of the pancreas by the intravenous injection of secretin were not entirely successful. However, in two cases the presence in the duodenum of large quantities of pancreatic enzymes was demonstrated. Indirect evidence against the existence of pancreatic insufficiency was the lack of a history of abdominal pain suggestive of pancreatitis, the absence of roentgenographic evidence of pancreatic calcification, the severe degree of diabetes, and the long interval by which the diabetes antedated the development of diarrhea.

In no case was the clinical picture that of nontropical sprue. Glossitis, edema, tetany, osteomalacia, and hypoprothrombinemia were all lacking, and there were neither spontaneous remissions nor therapeutic responses to diet, liver extract, or vitamins. Among the other disorders considered and excluded with reasonable certainty were Whipple's disease, fistulas or anastomotic operations which bypassed a large segment of intestine, liver disease with jaundice, regional enteritis, amebic colitis, and chronic ulcerative colitis. The lack of evidence of a primary disease process which was responsible for the gastrointestinal dysfunction in this group of cases with steatorrhea is in agreement with the absence of significant gross or microscopic abnormalities in a recent pathologic study of the intestinal tract in eight cases of diabetic diarrhea.[5]

In view of the reported relationship between visceral neuropathy and diabetic diarrhea, the possible role of neuropathy in the pathogenesis of the steatorrhea deserves careful consideration. Although the precise physiologic sequelae of sympathetic and parasympathetic denervation of the intestinal tract are not known, the importance of autonomic regulation of digestion, assimilation, and evacuation is generally accepted.[1,3,4,7,8,12,13] In each case of steatorrhea included in this report there was evidence of altered intestinal motility with a decrease in transit time of food particles, a deficiency

pattern on roentgenologic examination, or both. In each case there was also evidence of autonomic neuropathy. Because of the lack of specificity of many of the subjective evidences of autonomic disturbances, however, the precise time relationship between the onset of neuropathy and the onset of steatorrhea could not be determined. In most of the cases, the diarrhea antedated the subjective phenomena of impotence, postural dizziness, vesical dysfunction, neuritic pains, and paresthesias. However, this observation does not exclude earlier, and otherwise asymptomatic, autonomic neuropathy involving the intestinal tract which was etiologically related to the steatorrhea. Conversely, neuropathy secondary to nutritional deficiencies induced by the steatorrhea has not been excluded, but this sequence of events seems unlikely in view of the not uncommon occurrence of neuropathy in diabetic patients who do not have disturbances of gastrointestinal function.

It is of interest in this regard that in two additional cases steatorrhea was associated with severe diabetes in the absence of definite evidence of diabetic neuropathy. In one of the cases, gastrointestinal symptoms similar to those recorded above occurred in a 31-year-old woman 5 years after the onset of brittle diabetes. Extensive neurologic studies, including postural blood-pressure studies and a sweating test, were normal, and analysis of the duodenal contents provided evidence of adequate pancreatic exocrine secretion. In another case, similar gastrointestinal symptoms appeared in a 31-year-old man 7 years after the onset of severe diabetes. An extensive neurologic investigation was not performed; the finding of diminished reflexes in the lower extremities was not sufficient evidence for a diagnosis of diabetic neuropathy. In these two cases there is no evidence to support a neurogenic origin of the steatorrhea, although functionally significant visceral neuropathy involving only the intestinal tract could not be excluded.

SUMMARY

Six cases of intractable steatorrhea complicating severe, long-standing diabetes mellitus with neuropathy have been reported. The symptoms of diarrhea characterized by postprandial and nocturnal exacerbations and by nocturnal fecal incontinence were similar to those previously reported in cases of diabetic diarrhea. The clinical picture was not that of external pancreatic insufficiency, nor was there evidence of other disorders characterized by steatorrhea, such as nontropical sprue, Whipple's disease, or entero-enteric fistulas or anastomoses. In all six instances there was definite evidence of diabetic neuropathy involving the autonomic nervous system. The possible etiologic role of autonomic neuropathy involving the gastrointestinal tract has been discussed.

SUMMARIO IN INTERLINGUA

Steatorrhea Como Complication de Diabete Mellite con Neuropathia: Reporto de Casos sin Apparente Insufficientia Pancreatic

Es reportate 6 casos de steatorrhea intractabile, occurrente como complication de sever diabete mellite a longe durantia con neuropathia. Le symptomas de diarrhea characterisate per exacerbationes postprandial e nocturne e per nocturne incontinentia fecal esseva simple al symptomas previemente reportate in casos de diarrhea diabetic. Le aspectos clinic non suggereva externe insufficientia pancreatic, e nulle signos esseva notate de altere disordines characterisate per steatorrhea, como sprue nontropic, morbo de Whipple, o entero-enteric fistulas o anastomoses. In omne 6 casos signos esseva presente de neuropathia diabetic afficiente le autonome systema nervose. Es discutite le possibile signification etiologic de neuropathia autonome que involve le vias gastrointestinal.

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DISCUSSIONS

HENRY T. RICKETTS, M.D., (*Chicago*): I wonder whether the possibility has been considered that serum lipids are excreted into the bowel. This is known to occur in the normal bowel; the amounts of fats which are thus excreted are usually quite small. It seems to me unlikely, I must confess, that any excretion or secretion of lipids into the intestine could be of sufficient degree to account for the large amounts of fat found in these stools. I am led, however, to ask the question whether there seemed to be any relationship between the amount of steatorrhea and the levels of serum lipids in these patients.

DAVID ADLERSBERG, M.D., (*New York*): It is of great practical importance to study the diarrhea of diabetes and to separate the entities which are probably included under this term. I believe that I have seen cases similar to those presented by Dr. Berge. I should like to cite one case in which a remarkable therapeutic result was achieved. The patient was a woman of forty-one, who has had diabetes for thirty years, since the age of eleven. For seventeen years she has had diarrhea, mostly in bouts; the last one lasted for over a year, and resulted in loss of seventy pounds in weight. She had steatorrhea with 44 per cent of fat in the dry fecal material and other evidences of nontropical sprue. She was treated with cortisone. The diarrhea stopped; she gained fifty-three pounds in weight. At the same time, her insulin requirement increased considerably; she now has to take instead of 15 units 65 to 70 units of insulin. But she is healthy to the extent that she has one bowel movement a day, and she can work.

May I ask, Dr. Berge, if dilatation and thinning of the walls of the intestine, as occasionally seen in nontropical sprue, were found in the case which came to autopsy.

Secondly, I should like to know what the serum calcium and proteins were.

DR. BERGE: In reply to Dr. Ricketts' suggestion concerning fats in the blood, these were determined in several of the cases; hyperlipemia was not present in any. As he mentioned, the large amount of fat in the stools, in some instances over more than 50 gm. a day, would probably support the idea that this fat does not enter the bowel entirely from the circulation.

In response to the question concerning the use of cortisone in treatment, I should like to say that cortisone was tried in one of our cases, but it provided no benefit whatsoever.

The possibility of coexistent nontropical sprue was strongly considered in each case. The clinical picture, however, was not that of nontropical sprue and, except for steatorrhea, laboratory evidence in support of this diagnosis was usually lacking.

With respect to the necropsy findings, one patient was examined in a hospital in his home town, and tissue for examination has not been available to us. However, it was reported to us in a detailed manner by the pathologist that significant changes were not present in the intestinal tract, including the pancreas.

JOSEPH I. GOODMAN, M.D., (*Cleveland Heights, Ohio*): In view of the unusual rarity of the steatorrhea in the literature, I should like to ask Dr. Berge about the incidence of steatorrhea among the other diabetic diarrheas encountered.

DR. BERGE: Dr. Goodman, I am afraid I cannot give you a definite answer regarding the incidence of either diabetic steatorrhea or diabetic diarrhea. It is our impression, however, that of the two disorders, steatorrhea is the rarer. The incidence of diabetic steatorrhea, I am sure, would depend in part on how careful a search was made for the condition.

Prosthetic Technics in the Aftercare of Diabetic Gangrene

Ewen Downie, M.D., and Maida O'Connor,† Melbourne, Australia*

This paper describes an appliance, modified from the original design of Charlesworth,[1] which in our hands has found particular application to problems which have arisen from the conservative management of infection or gangrene in the feet of diabetic patients. These are complications of an aging population which has suffered peculiar nervous and vascular damage ofttimes for years before any typical symptoms or signs of trouble develop.

In recent years the introduction of antibiotic drugs has provided a choice of potent weapons to combat infections which previously were impossible to control except by drastic and radical surgery. In consequence conservative surgical procedures may now be undertaken which, without the help of these drugs, would still be unthinkable. It is important to realize that the treatment of the traumatic injuries of youth or early adult life differs sharply from that of the elderly diabetic. In the young adult loss of a leg below the knee can be almost completely compensated by the fitting of an adequate artificial limb, but in our experience very few patients over the age of sixty years will tolerate an artificial leg satisfactorily. This being so, a crutch is an inadequate and precarious substitute for a human limb. One fall from inexperience and the patient, losing confidence, prefers to spend the rest of his life in a wheel chair.

Radical amputation of the leg should be reserved for those cases in which overwhelming infection threatens life or where infection has progressed beyond the anatomical confines of the foot and has become impossible to control; for those cases in which tissue destruction has progressed to such an extent as to make any workable restoration of the foot impossible, and finally for those rare cases where prolonged, persistent and intractable pain demands relief. In all other cases every effort should be made to treat infection and gangrene on conservative lines, and to provide the patient with an animated stump, no matter how anatomically grotesque it may be, for we know of no substitute as effective in aging people.

Together with rigid control of the patient's diabetic state and the maintenance of normoglycemia, conservative procedures such as the adequate drainage of infection, the elective amputation of one or more toes and the complete debridement of dead and dying tissue will often permit healing. Apart from the parenteral use of appropriate antibiotic drugs, their local application to infected areas has much to commend it. Frequently the major arterial supply to the foot is gravely impaired and the concentration of any antibiotic which is given parenterally, in the area where it is most needed, is small. Accordingly the continuous topical application of an appropriate drug by means of a fine perforated polythene tube inserted into the affected area has proved a valuable means of ensuring the maximal benefit from antibiotic therapy.

The end results of such conservative procedures often present problems in the aftercare of the healed stump which, from its very nature, is subject to pressure when attempts are made to fit the patient with a shoe. Taking the simplest example of this problem, namely an elective transmetatarsal amputation of the foot, McKittrick and McKittrick[2] in their classic paper reporting over two hundred cases discuss this matter in the following words: "With but few exceptions these patients have been discharged from hospital without any special type of shoe. The toe of the shoe of the amputated foot has been filled with lamb's wool to lessen the tendency of the shortened foot to slip forward. Three patients with unilateral transmetatarsal amputations have had special inner soles made and report they are very satisfactory. They consist of a flexible steel plate with the space which the forefoot would have occupied filled with rubber foam."

After some years of filling the forepart of shoes with lamb's wool, latex, sponge rubber and so forth it was our experience that it was not possible in many instances to prevent the shift of such feet within shoes and so to prevent the development of callosities or ulceration. This particularly was so in conservative procedures which left a less well-defined stump than that of a transmetatarsal amputation, and which involved not only the loss of toes but in addition the loss of some metatarsal heads and shafts. With such cases it was necessary to devise technics which aimed to restore true body balance and

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freedom in walking. These will be described under two headings and later the application of these technics will be illustrated by reference to the records of three patients who presented particular problems.

1. *The slipper prosthesis*

Both feet of the patient are cast by winding a plaster bandage over the foot, allowing it to set and then cutting this off. From these shells, positive casts of the feet are made. The cast of the normal foot is subsequently used as guide for building the prosthesis for the affected foot. The cast of the stump is then covered with chamois leather. Four seams are formed at the corners and pinned securely to pull the chamois skin tight. The excess skin is then trimmed off, the pins removed and the seam folded out flat. The edges are then brushed with a clear rubber solution and pressed together with the fingers for a few minutes until the solution has set. When all seams have been treated thus they are cut level with the cast and pressed smooth with the hand. Strips of gauze bandage are then cut to the length of the seams, brushed with solution and pressed over the seams to reinforce them. Two lengths of bandage are then fixed with solution round the cast ½ inch up the dorsal surface. These prevent stretching of the chamois skin. Strips of latex foam ½ inch by 4 or 5 inches are then fixed to the forepart of the chamois and to each other by solution and pressure. When necessary, extra layers are added to the plantar or dorsal surfaces to protect any possible pressure points. The actual fashioning of the prosthesis varies with each case. Finally a sufficient number of layers of latex are added to form the missing toes. When firmly set, the prosthesis is shaped using the cast of the sound foot as a model. The normal cast is measured in four places: the length from the great toe to the heel and from the fifth toe to the heel; the depth through the first metatarsal head and through the fifth metatarsal head. The rubber is then cut with curved scissors and shaped to the pattern of the normal foot.

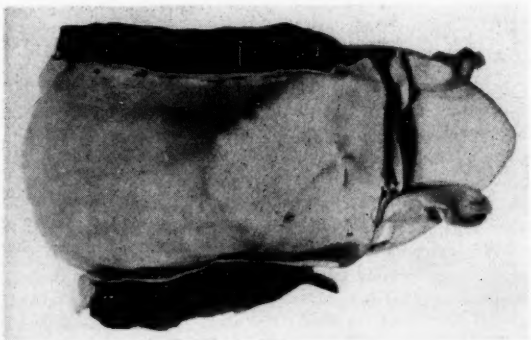


FIG. 1. Foundation chamois lining applied to cast.

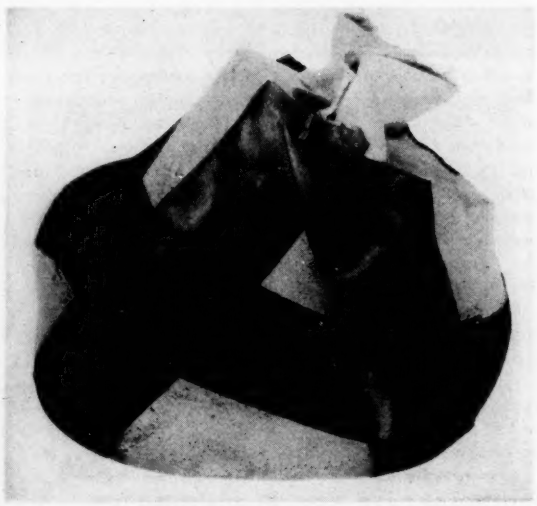


FIG. 2. Laminated sealing of seams of lining.

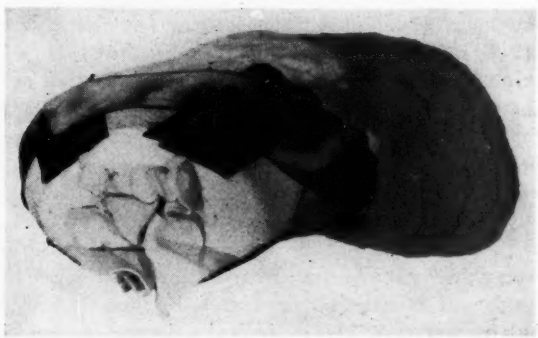


FIG. 3. Addition of layers of latex foam rubber before shaping.

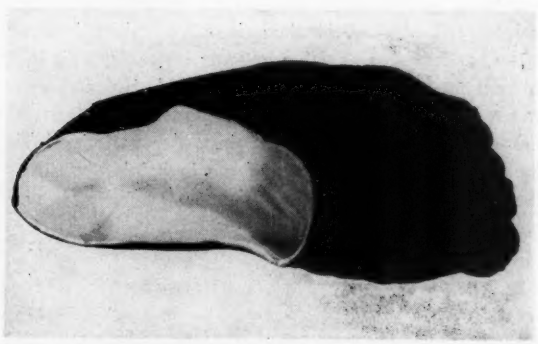


FIG. 4. Prosthesis after shaping and application of "skiva" skin.

The prosthesis is then finished with the application of an outer leather covering. A "skiva skin"* is cut into a large U shape taking the outline from the built-up cast. The underlap of the skin is folded on to the plantar surface and a small U is cut from the top to fold round the tarsal area. The inner surface of the skin and the dorsal area of the prosthesis are covered with clear rubber solution and the skin is smoothed on, taking care to avoid any creasing or ridging. The sole is then painted with solution and the underlap is folded and pressed into position finishing with a seam at the center back of the heel. A small oval piece of the skin is cut and fixed over the heel seam to seal it. Finally, the sole of the prosthesis is covered with a piece of "skiva skin" cut to the appropriate size and fixed on with solution. When the prosthesis is thoroughly dry (at least twelve hours is required for this) it is cut round the throat of the foot, at the level of the bandage, and is slipped off the cast and the edges neatly trimmed. It is then ready to apply to the patient's stump.

2. *Modification of shoes and boots*

With many patients who have experienced conservative surgery some modification of the shoe or boot worn on the affected foot is often a useful adjunct to the prosthesis just described. Although each patient has to be studied individually, two principles can be applied. These relate to the provision of some form of bar attached to the shoe in order to allow forward movement of the foot in the act of walking, and to modifications of the heel of the shoe in order to correct any tendency to inversion or eversion of the foot.

Two types of bar have proved to be effective, depending upon the nature of the individual problems encountered. First, a convex rocker bar which is an elongated convex bar built on to the sole of the shoe from ½ inch in front of the base of the heel and carried forward for an appropriate distance towards the ball of the foot. The size and extent of this bar depends on the problem presented by each individual patient and also upon the height of the heel of the shoe. Secondly, a domed metatarsal bar has been of value in some instances. This bar is built up in the waist of the shoe and shaped downwards to a finishing point just behind the metatarsal heads. It is raised 1/8 to 3/16 inch above the level of the normal sole. This bar is of use in helping to carry the body weight back to the tarsal area and gives better balance and firmness in walking.

In some instances where eversion of the stump occurs, it has been found that buttressing of the heel with an extension of the inner side has proved a valuable addition to the fitting of either a convex or a domed metatarsal bar. In general, it has been found that the Derby design of shoe or boot with a low or medium heel has proved the most satisfactory. The modifications just described can be easily fitted to them.

The records of three patients illustrate some applications of the technics already described.

CASE REPORTS

Case 1. A man, aged 68 years, attended the Diabetic Clinic in 1951 suffering with dry gangrene of the second and third toes of the left foot. The great toe of this foot had been amputated several years before this. An elective transmetatarsal amputation of the four remaining toes was performed and the stump healed satisfactorily in a period of two to three weeks. Subsequent to operation it was found that he walked with both feet everted and because of the loss of toes pronation was increased in the left foot. A slipper prosthesis was made with compressed felt and latex foam built into the longitudinal arch. The boot for his left foot was fitted with a domed bar and the heel was extended forward ½ inch on the inner side and wedged 3/16 inch with a ¼ inch buttress. He walks with the greatest of ease and can cover distances of several miles without discomfort.

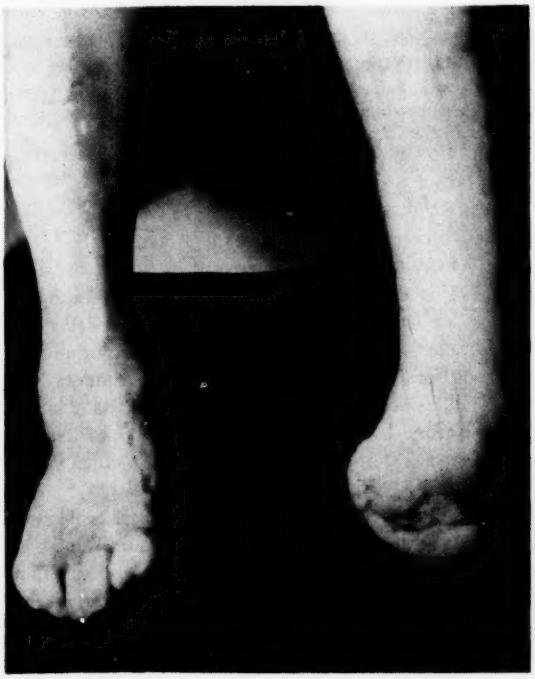
Case 2. A man, aged 63 years, was admitted to Alfred Hospital in 1952 suffering with cellulitis of the left foot and an infected gangrene of the second toe. Twelve months before, a mid-thigh amputation had been performed elsewhere for diabetic gangrene of the right foot. With conservative measures the infection in the left foot subsided and amputation of the second toe was performed six weeks after his admission. Soon after, he showed unmistakable evidence of spread of infection into the sole of the foot with involvement of the plantar fascia. In a desperate attempt to save the foot, extensive incision with adequate debridement was performed and continuous instillation of antibiotics directly into the affected area was commenced. The infection gradually subsided within the next three months. It was then possible to perform a further conservative operation. The third, fourth and fifth toes were removed with portions of the corresponding metatarsal bones. The great toe, which was unaffected, was left, as it was thought that in a man with only one leg it would lend stability to the stump which would have great responsibility for weight bearing. After ten months in hospital the left foot was soundly healed. A slipper prosthesis was made with a glove-like compartment for the great toe, and the metatarsal area was laminated with a layer of ¼ inch latex and compressed felt added to give more firmness in the longitudinal arch. An artificial limb was fitted to the mid-thigh stump of the right leg and ordinary shoes were fitted to both feet. It was thought that any form of bar on the left shoe would prove difficult to manage. At the time of his discharge from hospital this man was walking surprisingly well with the aid of one stick. A few months later he suffered a cerebral thrombosis with hemiplegia and died soon afterwards.

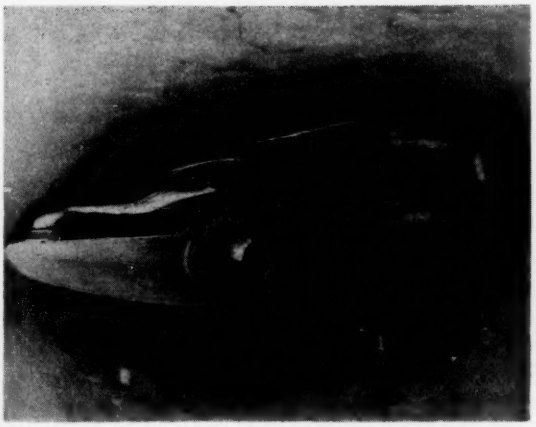
Case 3. A female, age 65, presented some unusual problems. Over twenty years before, she was involved in a motorcar accident and subsequently developed unilateral Parkinson's syn-

*A technical term for leather that has been "skived," i.e., the rough inner surface has been scraped with a knife in order to reduce the thickness and render it more flexible.

drome affecting the left arm and leg. This has not progressed but some tremor and rigidity of the arm and leg have been present for many years. Diabetes mellitus developed fifteen years ago. In 1947 she was seen with an area of soft undemarcated gangrene on the sole of the right foot at the site of a callus under the ball of the great toe. X-ray examination revealed osteomyelitis affecting the proximal phalanx and the head of the first metatarsal bone. With adequate incision and drainage together with local antibiotic therapy the foot healed with ankylosis of the affected joint and has given no trouble since.

In 1951 an infection of the left foot developed in the region of the head of the fifth metatarsal bone which arose from the paring of a callus on the sole of the foot. With rest and antibiotic therapy this subsided. At the time there was no radiological evidence of involvement of any bones in the foot. One year later trouble developed in the same area and this time there was definite evidence of osteomyelitis of the head of the fifth metatarsal bone. The fifth toe and the head of the metatarsal were removed but the operation area failed to heal. An infection of the great toe of the left foot with bone involvement also appeared and this toe was removed. For some





Case 3 illustrating formation, fitting and wearing of a prosthesis in this patient.

months thereafter infection persisted in both operation scars. In June 1953, X-ray plates suggested that there was low-grade osteomyelitis occurring in the heads of the remaining metatarsal bones. The degree of soft tissue and bony destruction was sufficient to prohibit a transmetatarsal amputation. It was believed that this woman would never be able to tolerate any form of artificial limb or to use a crutch because of the tremor of the left arm and leg. Accordingly it was decided to amputate through the cuneiform and cuboid articulations and to remove all the metatarsal bones. This was done and after a few weeks all evidence of infection subsided in the stump which has now been soundly healed for over a year. A slipper prosthesis was built to give support under the subastragaloid area. The left shoe has been fitted with an extended heel on the lateral side and buttressed appropriately. Despite her infirmities this woman is now capable of performing her own household duties without the aid of a stick and has recently commenced gardening.

SUMMARY

An appliance, modified from the pattern of Charlesworth, is described. This has proved of considerable use in solving problems arising from the conservative management of infection or gangrene of the feet. A brief account of conservative management is given. This is followed by a detailed description of the construction of a slipper prosthesis. Modification of shoes and boots used in conjunction with the prosthesis are then considered. Application of the prosthesis to clinical problems is illustrated by reference to three patients each of whom illustrates a particular application of these technics.

SUMMARIO IN INTERLINGUA

Technicas Prosthetic in le Post-Cura de Gangrena Diabetic

Es describite un apparato, modificate ab illo de Charlesworth. Iste apparato se ha provate utilissime in le solution de problemas que resulta ab le tractamento conservative de infection o gangrena del pedes. Es presentate un breve delineation del tractamento conservative. Isto es sequite per un description detaliate del construction de un prosthese calceiforme. Postea es considerate le modificationes del calceatura que es usate in conjunction con le prosthese. Le application del prosthese a problemas clinic es illustrate per tres casos representante tres specific utilisationes del technica.

REFERENCES

[1]Charlesworth, F.: Chiropodial Orthopaedics. Edinburgh, Livingston, Chap. VI, p. 90, 1951.

[2]McKittrick, L. S., McKittrick, J. B., and Risley, T. S.: Transmetatarsal amputation for infection of gangrene in patients with diabetes mellitus. Ann. Surg. *130*:826, October 1949.

DISCUSSIONS

CECIL STRIKER, M.D., (*Cincinnati*): What happens to the weight-bearing surface? Does it break down?

DR. DOWNIE: I think the answer to that is no. The prosthesis is designed to fit the foot, and the weight-bearing surface is comfortably held against the latex, on which there is no great friction. The whole purpose of this prosthesis is to fit the stump. We have never had any trouble since we started using this. We had a lot of trouble before, by just poking lamb's wool into the toe of the shoe.

ARTHUR R. COLWELL, M.D., (*Chicago*): Dr. Downie's remarks remind me that the medical profession is behind the dental profession in their resourcefulness in planning this type of device. I should like to thank him for bringing this to our attention, and for being willing to appear before us in this country.

The Effect of its Physical State on the Digestibility of Food

The completeness with which a food is utilized depends somewhat on its physical state; hence the advantage of cooking. This is illustrated in experiments of Rose and MacLeod, who compared the digestibility of raw egg white with that of cooked egg white. They found that in the same diet the coefficients of digestibility were 80 per cent for the one and 86 per cent for the other. The more recent studies of Hosoi indicate that raw egg white runs through the digestive tract so rapidly that it escapes digestion. Rose and MacLeod found that this food is more completely utilized when it is beaten, and Hosoi observed that its addition to milk resulted in a mixture which was better digested than either food alone.

From the book *Nutrition and Diet in Health and Disease* by James S. McLester, M.D., and William J. Darby, M.D., Ph.D. Philadelphia, W. B. Saunders Co., 1952, 6th ed., p. 136.

Experimental Diabetic Glomerulosclerosis

J. M. B. Bloodworth, Jr., M.D.,‡ and George J. Hamwi, M.D.,§ Columbus, Ohio

INTRODUCTION

With the advent of adequate replacement therapy for diabetes mellitus and the subsequent prolongation of life, degenerative vascular disease has become a problem of paramount importance. Unfortunately the study of degenerative vascular disease is complicated by its chronicity. The nodular glomerular lesions described by Kimmelstiel and Wilson[1] in 1936 remain obscure in origin, but—if critical histologic criteria are met—represent a form of degenerative vascular disease seen only in patients with diabetes mellitus. The study of these lesions as well as of degenerative vascular disease in general would benefit greatly by the availability of an experimental method for the rapid production of diabetic glomerulosclerosis. In 1951 Rich et al[2] reported that rabbits treated with cortisone for three weeks developed nodular glomerular lesions. Following this report we undertook the study of glomerular changes produced by the administration of various adrenal cortical steroids in the hope that we might produce typical diabetic glomerulosclerosis.

MATERIALS AND METHODS

Young adult male rabbits weighing initially 2,000 to 3,000 gm. were given stock rabbit pellets from which the "antibiotic-vitamin B_{12} supplement" was removed.* They also received carrots once weekly. Approximately 5 mg. of Unrefined Chlortetracycline† were given daily in the drinking water. Individual metabolism cages were used throughout the study and 24 hour urines were collected. Urinary protein was determined with 3 per cent sulfosalicylic acid. Urinary glucose was measured with Clinitest tablets® (Ames Company, Inc.); 4+ urines were measured quantitatively by the method of Benedict.[3] Blood glucose determinations were done by the method of Folin and Wu[4] and the blood total cholesterol by the method of Sackett.[5] Blood pressures were measured by the application of an ear cuff to the central artery.[6] Tissues were formalin fixed. In some animals diabetes was produced by the administration of 100 mg. per kg. of alloxan at weekly intervals until adequate glycosuria was obtained. All drugs were injected intramuscularly, once daily.

Acute Experiments: 21 to 60 Days

Previous studies in this laboratory have shown that the administration of cortisone acetate to the intact rabbit will induce prompt steroid diabetes and in 14 to 21 days moderately severe proteinuria.[7] Concurrent with the onset of proteinuria glomerular lesions appear. The first change noted is capillary dilatation, frequently reaching a degree comparable to the microaneurysms seen in the retinal capillaries of diabetic patients (figure 1). Next, thrombi appear within these dilated capillaries. Sometimes these thrombi, which will subsequently be referred to as cortisone lesions, have a foamy or vacuolated appearance (figure 2), while other thrombi resemble hyaline balls (figure 3). These cortisone lesions contain variable quantities of lipid, and the nonvacuolated portion is fuchsino-

FIG. 1. Rabbit glomerulus: capillary dilatation (microaneurysms). Short-term cortisone therapy. Hematoxylin & eosin, X 255.

*Supplement-free Red Rose Rabbit Pellets supplied by John W. Eshelman & Sons, Circleville, Ohio.

†Veterinary Aureomycin,® Lederle.

Presented in part at the Fifteenth Annual Meeting of the American Diabetes Association in Atlantic City, June 5, 1955.

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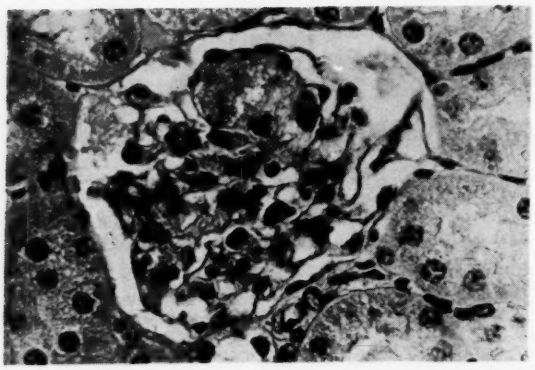

FIG. 2. Rabbit glomerulus: foamy and vacuolated capillary thrombi (cortisone lesion). Short-term cortisone therapy. Hematoxylin & eosin, X 300.

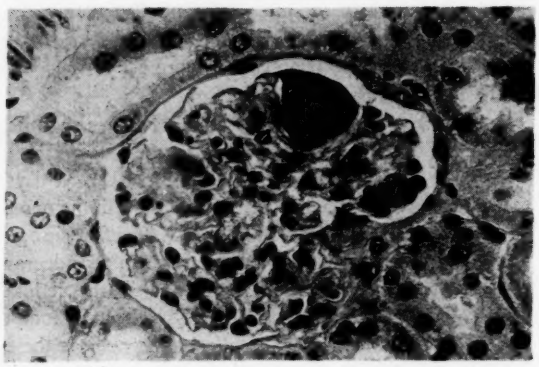

FIG. 3. Rabbit glomerulus: hyaline capillary thrombus (cortisone lesion). Short-term cortisone therapy. Hematoxylin & eosin, X 255.

philic when stained by the periodic acid-Schiff technic. The earliest lesion was discovered after 13 days of therapy. Almost all animals showed lesions after 21 days of cortisone administration. The lesions reached a numerical maximum after approximately 40 days of therapy and gradually diminished in number until very few lesions could be found after 60 days of cortisone administration. In many animals biopsies were taken after 30 days of therapy and the animals sacrificed one to two months later. At autopsy there were no definite changes attributable to the previously demonstrated cortisone lesions.

The administration of cortisone acetate to alloxan-diabetic rabbits produced results similar to those seen in the intact animal. With the instigation of cortisone therapy there was a prompt increase in the hyperglycemia and glycosuria. Proteinuria and glomerular lesions appeared after two to three weeks of therapy.

Other adrenal cortical steroids were given for a comparable period of time, 21-60 days (table 1).

When hydrocortisone acetate was administered to intact rabbits, the animals showed the same chemical and anatomic changes that were produced by cortisone. No conclusions can be drawn from the administration of hydrocortisone acetate to alloxan-diabetic rabbits since only two were treated.

The administration of 11-dehydro-corticosterone acetate to the intact rabbit produced no changes in carbohydrate metabolism. One animal showed mild proteinuria, probably not attributable to the drug. No glomerular changes were found.

When desoxycorticosterone acetate was administered to intact rabbits, there were no abnormalities in the carbo-

TABLE 1

The effect of adrenal cortical steroids on renal glomeruli, carbohydrate metabolism, and proteinuria in the rabbit. Acute experiments, 21-60 days

	Hormone	Number of rabbits	Hyperglycemia glycosuria (per cent)	Proteinuria (per cent)	Exudative lesions (per cent)
1.	Cortisone acetate, 5 mg./day	21	91	100	91
2.	Cortisone acetate, 10 mg./day	9	78	89	100
3.	Alloxan, 100 mg./kg. Cortisone acetate, 5 mg./day	6	100	100	84
4.	Alloxan, 100 mg./kg. Cortisone acetate, 10 mg./day	7	100	86	100
5.	Hydrocortisone acetate, 3 mg./day	3	100	100	100
6.	Hydrocortisone acetate, 5 mg./day	5	80	100	100
7.	Alloxan, 100 mg./kg. Hydrocortisone acetate, 5 mg./day	1	100	0	0
8.	Alloxan, 100 mg./kg. Hydrocortisone acetate, 7.5 mg./day	1	100	100	0
9.	11-dehydro-corticosterone acetate, 5 mg./day	2	0	0	0
10.	11-dehydro-corticosterone acetate, 10 mg./day	2	0	50	0
11.	Desoxycorticosterone acetate, 0.5 mg./day	3	0	66	0
12.	Alloxan, 100 mg./kg. Desoxycorticosterone acetate, 0.5 mg./day	2	100	100	0

hydrate metabolism. Two animals developed a mild proteinuria, probably not attributable to the drug. No glomerular changes were seen after one month of therapy. Two alloxan-diabetic rabbits also received desoxycorticosterone acetate. There was no effect upon the previously present hyperglycemia and glycosuria. Both animals developed proteinuria, but no glomerular lesions were present after one month of therapy.

Long-Term Studies

The changes produced by long-term administration of cortisone acetate and hydrocortisone acetate are similar. Animals were examined at varying periods after three to nine months of therapy. The glomeruli showed a gradual thickening of the supporting stroma which was PAS-positive but did not show definite nodularity. The changes are quite similar to those seen in control animals and attributable to aging. However, the hormone-treated animals showed changes of a much greater degree than those seen in control animals of comparable age.

The most striking result was produced by the administration of desoxycorticosterone acetate to an alloxan-diabetic rabbit. The blood pressure and chemical changes produced in this animal are shown in figure 4. Intermittent glycosuria was present throughout the course of therapy. Hyperglycemia was present during most of the course of therapy; terminally the fasting blood sugar was normal. A moderate proteinuria was present early in the course of desoxycorticosterone acetate therapy but then subsided. After approximately nine months of therapy severe proteinuria abruptly reappeared, reaching a level between 500 and 1,000 mg. per 100 cc. The blood pressure showed a slight elevation terminally. After the onset of proteinuria the total blood cholesterol also showed moderate elevation. Biopsies taken at one and four months showed normal glomeruli. However, when the animal was sacrificed one month after the onset of marked proteinuria and 332 days after the instigation of desoxycorticosterone acetate therapy, nodular lesions were found in almost every glomerulus (figure 5). These lesions were usually located peripherally in the glomerulus. They were eosinophilic, PAS-positive nodules, negative for lipid and glycogen, and when compared by numerous special stains resembled quite closely the typical nodular lesions of diabetic glomerulosclerosis.

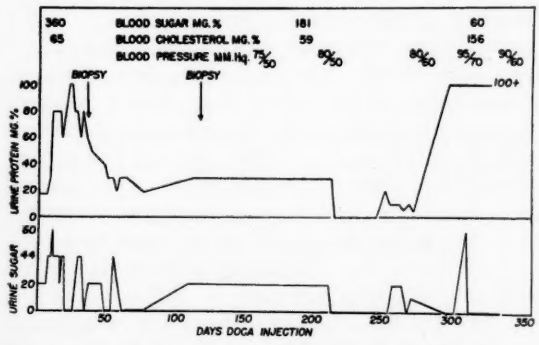

FIG. 4. The effect of long-term administration of desoxycorticosterone acetate to an alloxan-diabetic rabbit.

DISCUSSION

The typical nodular lesions described by Kimmelstiel and Wilson (figure 6) are limited to patients with diabetes mellitus—if critical histologic criteria are met. Because of the uncertainty of the location of these lesions we refer to them as *diabetic glomerulosclerosis.*[7a] They

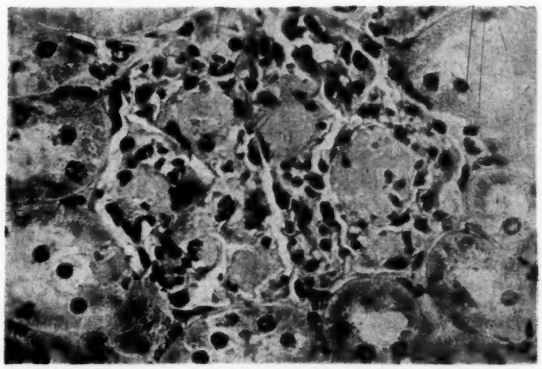

FIG. 5. Rabbit glomerulus: nodular glomerular lesions produced by the long-term administration of desoxycorticosterone acetate to an alloxan-diabetic rabbit (DOCA lesion). Hematoxylin & eosin, X 255.

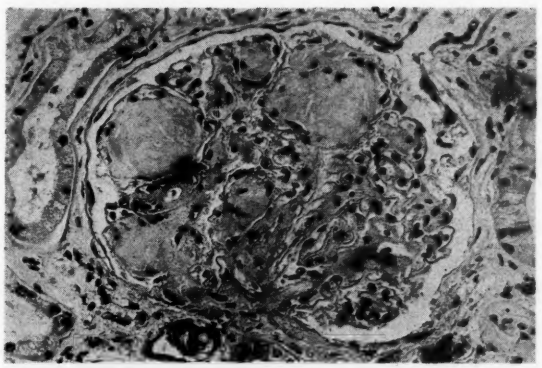

FIG. 6. Human glomerulus: diabetic glomerulosclerosis, the typical nodular lesions described by Kimmelstiel and Wilson. Hematoxylin & eosin, X 165.

are present in less than half of the patients with diabetes mellitus. Usually they are associated with a history of longstanding diabetes mellitus, frequently severe in de-

gree and often poorly controlled. Clinically there is usually amelioration of a previously severe diabetes, hypertension, proteinuria, and often the nephrotic syndrome.

One frequently sees a second type of glomerular change in association with the typical nodular lesions. These *exudative lesions* are occasionally seen in conditions other than diabetes mellitus. They consist of a combination of foamy or vacuolated eosinophilic lesions and homogeneous eosinophilic hyaline-like masses located in the periphery of the glomeruli (figure 7). Occasionally there is an associated eosinophilic material free in the space between the parietal and visceral layers of Bowman's capsule. These lesions have been described under many names.[8, 9, 10, 11] The term *hyaline-fibrinoid* has been used because of their hyaline nature and the similarity of their staining reactions to those of fibrinoid.[12] By diligent search these lesions can usually be found in all cases of diabetic glomerulosclerosis, but—in our experience—have been more frequent in rapidly progressive Kimmelstiel-Wilson syndrome with renal failure. It is interesting to speculate that these exudative lesions represent an early phase in the development of typical nodular lesions. However, there is little actual evidence to support this thesis. No transitional forms have been demonstrated, and the two lesions differ in many staining characteristics.

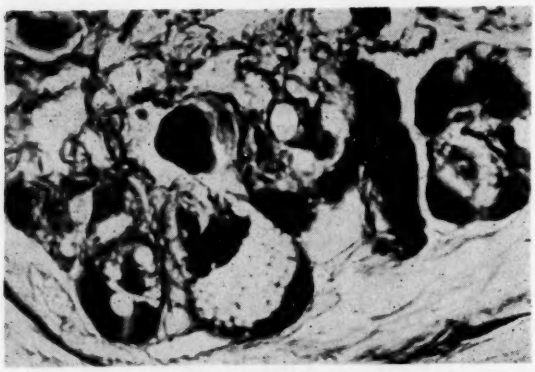

FIG. 7. Portion of human glomerulus: exudative lesions. Note the foamy, vacuolated and hyaline forms. Hematoxylin & eosin, X 590.

There is a striking similarity between the exudative lesions and the cortisone lesions described in this paper. The production of steroid diabetes by cortisone would seem to relate the cortisone lesions to diabetes mellitus. The concurrent production of proteinuria and glomerular lesions by cortisone similates the sequence of events in the Kimmelstiel-Wilson syndrome. However, the cortisone lesions have not progressed to typical nodular lesions even after long-term administration of cortisone. In fact these lesions seem to disappear, possibly by lysis of the thrombi. Certainly no residual damage has been demonstrated following the production of these lesions. At present one must assume that the cortisone lesions are acute changes which occur in association with steroid diabetes and proteinuria but that they do not seem to progress to the typical nodular lesions of diabetic glomerulosclerosis.

There has been a great deal of speculation concerning the nature of these cortisone lesions. Some authors believe that the capillary dilatation is secondary to thrombosis. Wilens and Stumpf[13] have stressed the importance of lipid in the production of the cortisone lesions. They pointed out that the cholesterol, phospholipid and neutral fat were all elevated by the administration of cortisone. On the other hand, when cholesterol was administered in addition to cortisone there was no increase in the number of glomerular lesions despite a further increase in the level of all three lipid fractions. Our rabbits also showed a rise in the cholesterol and neutral fat. However, the changes were erratic: some animals did not show the changes; in other animals the elevated cholesterol and neutral fats had returned to normal levels before the cortisone lesions appeared. There is no doubt that the cortisone lesions contain variable but consistent quantities of lipid and that lipids play an important part in their pathogenesis, but to date we have not shown a direct relationship between the lesions and any specific lipid fraction. Our studies in this field are continuing. Rosen et al[14] reported that heparin administration reduced both the lipemia and the number of glomerular lesions in cortisone-treated rabbits. On the other hand, Wilens and Stumpf[15] were unable to confirm this finding. Confusing the picture further, Hartroft[16] has described lesions in choline-deficient rats which begin as lipid plugs and later develop into lesions which closely simulate diabetic glomerulosclerosis in man.

The administration of desoxycorticosterone acetate is known to produce numerous anatomic changes in the kidney. These changes are associated with retention of sodium and chloride, loss of potassium, edema, hypertension and often cardiac failure. Selye[17] showed that there was an increase in the weight of the kidneys. He demonstrated vascular changes in chicks receiving only desoxycorticosterone acetate.[18] In other species (dog, monkey, rat) salt loading or salt loading plus unilateral nephrectomy were used to sensitize the animals receiving desoxycorticosterone acetate. The glomerular lesions consisted of cellular proliferation, deposition of hyaline material in the tuft, and the occasional appearance of eosinophilic material in the lumen of Bowman's capsule. The occurrence of homogeneous pale eosinophilic nodules similiar

to the lesions of diabetic glomerulosclerosis was not reported. When renin plus desoxycorticosterone acetate were administered to uninephrectomized rats receiving 1 per cent NaCl for drinking water, more severe glomerular lesions were produced with frequent foci of necrosis and occasional vacuolated hyaline thrombi.[19] Still there were no lesions which resembled the typical nodular lesions of diabetic glomerulosclerosis.

We administered desoxycorticosterone acetate to two alloxan-diabetic rabbits. One animal succumbed after six months of therapy, while the other survived and showed marked proteinuria after nine months of therapy. The nodular glomerular lesions found at autopsy one month after the onset of proteinuria were quite similar to the typical nodular lesions of diabetic glomerulosclerosis. This rather unexpected development opens a new avenue of approach to the problem of experimental diabetic glomerulosclerosis. No conclusions can be made until this finding is confirmed. The production of DOCA lesions in additional rabbits and the study of the animals by histologic technics, chemistry, and electrophoresis are under way with the hope that these DOCA lesions may be more firmly established as experimental diabetic glomerulosclerosis.

SUMMARY

The administration of cortisone acetate or hydrocortisone acetate to normal rabbits produces glycosuria, and in fourteen to twenty-one days proteinuria and foamy vacuolated or hyaline glomerular lesions closely resembling the exudative lesions frequently seen in the human diabetic. These cortisone lesions are PAS-positive and contain variable quantities of lipid. They reach a maximum after forty days of therapy and then gradually decrease in number. No residual change has been observed.

Administration of cortisone acetate for longer periods, four to six months, produces a diffuse thickening of the glomerular stroma without nodularity.

The administration of desoxycorticosterone acetate to one alloxan-diabetic rabbit produced marked proteinuria after nine months of therapy, and when the animal was sacrificed one month later nodular lesions were present in most of the glomeruli. The DOCA lesions were pale eosinophilic homogeneous masses located in the periphery of the glomeruli. They were PAS-positive but contained neither lipid nor glycogen. Special staining reactions also showed a similarity to the typical nodular lesions of human diabetic glomerulosclerosis.

SUMMARIO IN INTERLINGUA

Glomerulosclerosis Diabetic Experimental

Le administration de acetato de cortisona o de acetato de hydrocortisona a conilios normal produce glycosuria e, intra duo o tres septimanas, proteinuria e scumose vacuolate o hyalin lesiones glomerular de alte similitude al lesiones exsudative que es vidite frequentemente in diabeticos human. Iste lesiones de cortisona es positive a acido para-aminosalicylic e contine quantitates variabile de lipido. Illos attinge lor maximo post quaranta dies de therapia e postea reduce lor numeros gradualmente. Nulle alteration residue ha essite observate.

Le administration de acetato de cortisona durante plus longe periodos (quatro a sex menses), produce un diffuse spissification del stroma glomerular sin nodularitate.

Le administration de acetato de disoxycorticosterona a un conilio alloxano-diabetic produceva marcate proteinuria post nove menses de therapia. Quando le animal esseva sacrificate un mense plus tarde, lesiones nodular esseva presente in le majoritate del glomerulos. Le lesiones de acetato de disoxycorticosterona esseva pallide massas homogenee eosinophilic locate in le peripheria del glomerulos. Illos esseva positive a acido para-aminosalicylic sed contineva ni lipido ni glycogeno. Special reactiones de coloration etiam exhibiva un similitude al typic lesiones nodular de glomerulosclerosis diabetic human.

ACKNOWLEDGMENTS

We wish to express appreciation to Miss Suzanne Beck and to Dr. Hollis Lougheed, D.V.M., for technical assistance, to Mr. R. A. Flummerfelt and his staff for the special stains, and to Mr. Gilford Millard for the photography. We are indebted to Dr. Elmer Alpert of Merck and Co. for cortisone and hydrocortisone, to Dr. Augustus Gibson of Merck and Co. for the 11-dehydro-corticosterone acetate, and to Dr. R. L. Burkhardt of Lederle Laboratories for the veterinary Aureomycin.®

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DISCUSSIONS

E. T. BELL, M.D., (*Minneapolis*): The glomerular lesions in the rabbit which Dr. Bloodworth showed us resemble human nephrosclerosis. However, one fundamental difference is noted. In the human lesion, there is invariably a severe hyaline arteriosclerosis in the afferent arteriole and often in the efferent arteriole. I did not see this in any of the slides; that is why I do not believe that this is a complete reproduction of the Kimmelstiel-Wilson lesion.

J. M. B. BLOODWORTH, JR., M.D., (*Columbus, Ohio*): I must stress that we ourselves have not yet accepted these experimental glomerular lesions as identical with the typical nodular lesions of diabetic glomerulosclerosis. We have produced the experimental lesions in only one animal and this animal was sacrificed quite shortly after the onset of severe proteinuria. We are continuing this study and hope that, by maintaining similar animals for a longer period after the development of proteinuria, we may produce more typical changes.

HAROLD RIFKIN, M.D., (*New York, New York*): In view of the fact that glomerular changes may be responses to a variety of noxious agents, it would be important to know if you found typical aneurysms in the rabbits' ocular fundi like those we see in patients with diabetic retinopathy.

DR. BLOODWORTH: I did not hear the first part of your question. As far as the micro-aneurysms in the eye are concerned, we have done quite a few flat preparations of the retina stained by the Hotchkiss-McManus technic. We are quite successful in our human preparations and have seen many retinal aneurysms. In the rabbit, we have never been able to identify a microaneurysm. I have written Dr. Becker about this problem, and he replied that his original lesions were produced "only in an occasional animal," and only in those receiving ACTH.

A. LAWRENCE CHUTE, M.D., (*Toronto, Canada*): I think you must consider the possibility that the alloxan has done something here, too. In some similar work on alloxanized rats some years ago, feeding them large amounts of salt, we found we got rather similar changes, and also vascular changes as well.

However, if we clamp the renal arteries at the time the alloxan is administered, so that we prevent any damage to the tubules of the kidney itself, we are unable to produce any of these results. I think we should make sure therefore that alloxan has not been a factor.

Also, it took some weeks for these lesions to develop.

DR. BLOODWORTH: That is, of course a possibility. We can say only that, on two surgical biopsies made on this particular animal with rather careful examination of every glomerulus in the sections, there was no evidence of any glomerular damage whatever at the end of four months of therapy. This actually was approximately five months after the administration of alloxan.

I might also point out that we administer alloxan in doses approximately one half of the usually recommended dosage of 200 mg. per kg. We administered 100 mg. per kg. and found that it was adequate to produce a low-grade glycosuria.

JOHN E. HOWARD, M.D., (*Baltimore*): It is rather happy, sometimes, to find that at least your speculation is that the human being resembles a rabbit more than the rat because, most of the time, it is the other way. (Laughter)

I was wondering if Dr. Bloodworth would tell us whether he had at any time stopped cortisone or hydrocortisone during the administration, at a time when he felt reasonably certain that these lesions must have occurred, to see in what phase, if any, these lesions might be reversible.

This is a fairly significant point, especially in view of the adrenal removals and hypophysectomy as therapy against such lesions. For if once there they don't disappear when the hormonal instigators are withdrawn, such operations would be contraindicated.

DR. BLOODWORTH: We did just that at the beginning of our study. That was alluded to in the statement that these lesions tend to disappear completely. We have found no specific residual damage. Apparently, these thrombi disappear, because we had a series of animals to which we administered cortisone for approximately 30 days, which we know will produce lesions in almost 100 per cent.

Some of these animals were biopsied surgically after 30 days of therapy and we found lesions. Then we stopped cortisone and waited two or three months before sacrificing the animals. At that time there was no change except for a thickening of the supporting stroma, which we have found to occur in all of our control animals. We feel that this thickening of the stroma is part of the aging process.

ARNOLD LAZAROW, M.D., (*Minneapolis*): I would like to ask whether the diet on which these animals have been kept has any bearing on the development of lesions. You will recall some of the earlier studies in which several investigators were unable to produce lesions in diabetic rabbits by administering steroids. Could dietary differences have been a factor in these failures?

In your rabbit studies using DOCA you reported lesions in one animal. How many other rabbits which were similarly treated with DOCA did not develop lesions? How much DOCA was used in these studies?

DR. BLOODWORTH: In answer to the first question, I was aware of this problem following a discussion with Dr. Becker, and I did obtain in my original work a supplement-free feed. We were using the Red Rose Rabbit Pellets of Eshelman & Sons from which they removed their so-called antibiotic-B_{12} supplement. We found that use of supplement-free feed was necessary to produce this 90 to 100 per cent result.

We still got lesions in perhaps 40 or 50 per cent of the animals who were on the standard feed containing the supplement. We have continued to investigate this problem and found that, at least, the simple administration of comparable quantities of Aureomycin in the drinking water, or vitamin B_{12} by injection, or a combination of the two drugs, has no effect on cortisone lesions. At the present time, we are not certain as to what the factor in this rather crude supplement is, or whether it is related to the route of drug administration.

Educational and Economic Hazards Imposed by Faddists

The direct economic waste caused by faddists and quacks, with their ill-advised sale and promotion of food materials, literature and lectures to the American public, is estimated to reach about $500,000,000 per year. However, that figure apparently does not represent the greatest damage caused by those who mislead the public by promotional schemes based on distorted information about foods and nutrition.

Their most destructive influence lies in the lies they propagate for their own gain. They become masters at creating surprise, confusion, and suspicions about common foodstuffs, and then follow with a great variety of clever ways to get the consumer's dollar before either the orderly processes of education or the long arm of the law can catch up with them.

The food faddist makes expert use of modern methods of communication to reach masses of people, ranging all the way from dramatic lectures with flood lights and loud speakers to radio, television and the press. There is a tragic weakness in our legal machinery for protection of the public against distortions of the truth. . . . The laws regulating food labeling and direct, printed advertising claims are relatively effective. But a fear of regulatory practices that imply actual or potential censorship places a great handicap on efforts to achieve respect for honesty in what people say or write.

I believe two types of action could be developed more effectively to curb unscrupulous faddists and quacks: first, through a greatly strengthened program of direct education of the public, and second, through more alert and sustained action by such voluntary bodies as the technical organizations in each community, and the Better Business Bureaus. The latter could, if alerted on a national scale and supported by the press, discredit most of the fake 'food experts.'

Charles Glen King, Ph.D., and Horace L. Sipple, Ph.D., from the Nutrition Foundation and Columbia University, New York City, in *Federation Proceedings* 13:794-96, September 1954.

Tautologous Diabetic Coma—A Behavior Syndrome

Multiple Unnecessary Episodes of Diabetic Coma

Franklin B. Peck, Sr., M.D., and Franklin B. Peck, Jr., M.D.,† Indianapolis*

The occurrence in a single patient of almost 50 repetitive instances of severe diabetic coma within 8 years of onset of the disease at age 12 is unique. Multiple comas of reasonable number are not unusual, but we know of no reported case having so many. The term tautologous has not been previously applied to diabetic coma. It is usually employed rhetorically, but in this instance it seems especially apropos, signifying as it does "needless repetition." The development of this behavior pattern is of special interest in relation to the effect of stressful situations on the control of diabetes and the influence of subsequent poor control on the development of vascular complications.

CASE HISTORY

The patient, (M.R.J.) 70896, a white female, aged 20, was first admitted to Indianapolis General Hospital in 1946 when she was 12 years old. She was unconscious, in deep diabetic keto-acidosis following three months of prodromal symptoms of hunger, thirst, and polyuria, with loss of 10 pounds in weight. Blood sugar was 500 mg. per cent, plasma carbon dioxide combining power 5 mEq./L., and Rabinowitch severity index 20[1] (very severe). In the ensuing 12 hours 500 units of insulin were required to restore normal metabolic equilibrium. During the succeeding days good balance was established. The patient's attitude was cooperative, and she quickly learned to calculate diets with such facility that she could assist the hospital dietitian in this capacity. She was discharged under good control, taking 16 units of protamine zinc insulin and 30 units of regular insulin each morning before breakfast, with diet C 225, P 80, F 75/1,895 calories, and instructed to return to the outpatient clinic for periodic recheck and guidance. Her course was uneventful through 1946-47.

An astonishing series of 35 episodes of severe coma then followed, supplemented by additional comas in other hospitals (table 1). Forty-two such episodes have actually been fully documented, and we have reason to believe there are several more not here recorded. She moved to another state in 1953 where only one episode occurred in a year and a half; then she returned to Indianapolis and was again admitted in coma in December 1954. The period 1952-53 was her championship year at Indianapolis General Hospital. It was featured by 18 admissions, an all-time record of well over one coma per month. In several instances the patient was desperately ill, having blood sugar levels ranging to 1,000 mg. per cent, extreme dehydration, and circulatory collapse. Each time recovery occurred and reasonably good control was re-established before discharge with doses of insulin ranging from 80 to 110 units daily. On each admission evidence of vascular damage and changes in ocular fundi were carefully sought but none was ever found.

Three weeks prior to the December 1954 admission to the hospital (comatose; pulse 130; blood pressure in right arm 140/80, in left arm 50/0; blood sugar 480 mg. per cent; plasma carbon dioxide 4.2 mEq./L.) careful history disclosed that she had noted the initial appearance of numbness, pallor, and coldness of the left hand and arm several months previously and had had two acute attacks. Examinations by Dr. K. R. Woolling, Department of Peripheral Vascular Diseases, established the absence of left brachial, radial, and ulnar pulsations. X ray confirmed the diagnosis of well established chronic occlusive arterial disease but did not disclose any calcification. The eye grounds remained normal. There was an obvious atrophy over the left upper extremity.

DISCUSSION

This patient is the product of a broken home. Her parents were divorced shortly before she was found to have diabetes. The mother has had eight convictions for child neglect, drunkenness, and immorality. The father was an alcoholic, her stepfather is the same: the latter has been jailed on numerous occasions for beating his wife. In 1947 the mother was sent to Woman's Prison, and it was at this time that the child began to have the tautologous comas. She was then living in a guardian's home, and this was followed by several foster homes with relatives. At any sign of friction the patient would run away and appear at the General Hospital in a few days in coma. There is evidence that the comatose state in certain instances, was deliberately induced and that it constituted a behavior pattern designed to meet an intolerable life situation. On one occasion, following a too frank discussion of this aspect of the problem by the senior author during a ward round with the resident staff, the patient left the hospital, transferred her alle-

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Presented at the Second Congress of the International Diabetes Federation in Cambridge, England, on July 6, 1955.

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†Resident in Medicine, Lilly Laboratories for Clinical Research, Indianapolis General Hospital.

TABLE 1
Hospital admissions

Date	Hospital	Blood sugar	Carbon dioxide mEq./L.	BUN	Blood pressure	Rabinowitch severity index	Urine acetone	Insulin first 12 hr.	Coma duration	Insulin on discharge
9/19–10/22/46	IGH	500	5	62	80/60	20	4+	500	13	51
5/26–6/8/47	IGH	435	2.7	60	120/70	11	4+	130	8½	70
8/4–9/27/47	IGH	140	22	30	120/74	<5	1+	75	3	75
10/17–10/26/47	IGH	381	6	33	118/60	12	4+	110	10	120
2/14–3/9/48	IGH	408	8.2	33	140/80	12	3+	260	11	140
6/12–6/28/48	IGH	444	13	30	130/70	7	4+	230	13	150
7/24–8/6/48	St. V.	514	—	25	120/80	>5	4+	150	—	135
9/9–9/17/48	IUMC	388	16	—	—	>7	4+	60	—	70
9/23–10/15/48	IUMC	500	20	30	—	8	4+	200	—	166
11/5–11/28/48	IUMC	520	3	—	130/70	10	4+	270	72	226
12/9–12/12/48	IUMC	400	—	—	115/90	<5	4+	60	48	226
12/23/48–1/24/49	IUMC	571	4	—	118/94	12	4+	130	24	158
2/15–3/11/49	IGH	430	4	38	126/90	12	4+	180	14	120
3/20–3/29/49	IGH	350	4	30	124/60	9	4+	260	12	130
4/4–5/17/49	IGH	512	6	34	114/78	5	4+	200	6	100
5/22–6/9/49	IGH	380	6	55	132/68	11	4+	170	17	110
6/14–6/25/49	IGH	218	4	30	130/70	13	4+	370	6	110
8/1–8/15/49	IGH	455	4	30	130/70	11	4+	300	10	160
8/18–9/9/49	IGH	500	4	—	138/80	10	4+	310	8	130
9/16–9/24/49	IGH	556	6	—	120/60	4	4+	120	7	130
10/10–10/22/49	IGH	470	4	—	118/80	5	4+	150	5	130
10/26–11/8/49	IGH	63	4	49	105/60	8	4+	80	10	115
11/14/49	IGH	37	18	—	140/70	—	neg.	0	2	—
12/6/49–1/4/50	IGH	530	4	25	134/76	12	4+	460	26	115
2/23–3/11/50	IGH	395	4	70	124/80	15	4+	340	13	140
5/20–5/27/50	IGH	525	6	—	120/70	8	4+	245	18	140
6/16–6/26/50	IGH	500	10	—	110/70	10	4+	120	11	130
7/14–7/19/50	IGH	800	12	35	130/70	5	4+	300	7	100
7/29–8/4/50	IGH	50	24	40	96/70	<5	4+	100	8	115
8/17–8/27/50	IGH	620	8	104	120/60	15	4+	80	11	115
9/22–9/29/50	IGH	50	12	29	110/90	11	4+	40	12	100
11/1–11/7/50	IGH	800	4	65	120/70	10	4+	280	11	120
11/12–11/19/50	IGH	110	11	—	100/65	5	4+	120	6	120
11/25–12/6/50	IGH	1175	5	—	100/60	14	4+	260	12	120
12/31/50–1/6/51	IGH	620	5	—	100/90	12	4+	340	16	120
2/23–3/17/51	IGH	767	4	26	135/80	9	4+	340	16	100
6/14–6/26/51	IGH	600	4	—	100/90	9	4+	160	12	120
11/29–12/21/51	IGH	740	4	21	120/70	11	4+	240	12	160
12/2–12/3/52	IGH	455	20	16	116/64	8	3+	80	8	80
2/16–2/20/53	IGH	415	8	6	115/50	9	4+	320	12	80
Out of state	B.G., Ky.	No records								
12/13–12/20/54	IGH	480	4	26	140/70	7	4+	320	8	100

giance to another institution, and there continued the repetitive course of events. Intensive psychotherapy over a period of three years was unsuccessful in effecting an adequate adjustment. An unpleasant stressful situation was met habitually by precipitation of a bout of acidosis and coma and removal from the life stress to the more sympathetic hospital environment. The patient apparently committed a kind of suicide at will, with the assurance that her demise would be temporary and not permanent. Uncertainty that the usual facilities were available to bring about her restoration was followed by a period while out of the state during which only one coma occurred.

The influence of emotional states on diabetes has long

been recognized. Mirsky[2] presented experimental evidence that hyperglycemia can be provoked in diabetic persons during psychiatric interviews. Hinkle and associates[3, 4] described two types of response to stress situation, one characterized by ketonemia but usually preceded by a fall in blood sugar level. If this occurs in a diabetic and is accompanied by "stress diuresis," this response may lead to ketosis. If the person is then given glucose the glucose tolerance curve is higher and more prolonged. Such a mechanism might well be the "trigger" activating the prompt development of severe diabetic comas in the present case.

The delayed development of vascular damage in spite of such dramatic persistent insults and poor control of the diabetes is also noteworthy. Approximately eight years of such tautologous behavior elapsed before positive findings occurred, and even then the eye grounds were not hemorrhagic. The long-term studies of the Joslin group, Keiding, Root, and associates[5, 6] suggest that vascular complications are related to the degree of control of diabetes; and that under ordinary circumstances they develop in 10 to 15 years even though control may be classified as generally excellent. Our patient has provided an opportunity to observe the effect of intensive and almost constant poor control and the influence of repetitive severe comas. The fact that peripheral occlusive vascular disease has had its onset and then developed rapidly since the patient's last admission in 1953 may be of some significance.

In January 1955, after the last described admission and following a series of discussions with the patient, the junior author arranged for her employment as an assistant in the diet kitchen at Indianapolis General Hospital. Here she would undertake supervised responsibilities for the calculation of diabetic diets and could participate in teaching dietary calculations to new diabetics and those undergoing treatment in the wards of the hospital. Contact with her immediate family was discontinued, and she now lives with an aunt who has a mature understanding of the problem. The value of this psychotherapy has been reflected in the state of diabetic control, in that it is uneventfully good and has manifested only rare glycosuria over these months, with a daily dose of 60 units of insulin.

SUMMARY

A behavior syndrome termed tautologous diabetic coma and occurring in a severe juvenile diabetic person is described. It is characterized by repetitive comatose states brought about in response to disturbing and intolerable situations in the patient's life environment. Approximately fifty episodes of coma have occurred in the course of eight years. The case is considered in relation to the effect of stressful situations on the control of diabetes and the effect of poor control on development of vascular complications. Improved social and emotional adjustment has been followed by a complete cessation of diabetic instability and comas.

SUMMARIO IN INTERLINGUA

Coma Diabetic Tautologe—Un Syndrome de Behavior: Multiple Episodios Innecessari de Coma Diabetic

Es describite sub le nomine de coma diabetic tautologe un syndrome de behavior occurrente in un juvene persona con sever diabete. Le syndrome esseva characterisate per repetite statos comatose provocate in responsa a disturbante e intolerabile situationes in le ambiente vital del patiente. Circa 50 episodios de coma occurreva in le curso de octo annos. Nos discute iste caso in relation al effectos de situationes stressante super le domination de diabete e le effectos de inadequate domination super le disveloppamento de complicationes vascular. In le caso hic presentate, le melioration del adjustamento social e emotional resultava in le complete cessation de comas e instabilitate diabetic.

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DISCUSSIONS

H. D. BREIDAHL, M.D., (*Australia*): I should like to thank Dr. Peck for his paper and for reporting this very interesting case. I am going to make a little note about the opposite condition, because one occasionally sees diabetics with behavior problems who present hypoglycemia, self-induced. These cases have been reported—I think the first one by Dr. Rynearson—and they do present similar behavior problems. They are often very diffi-

cult to cure, and Dr. Peck's patient certainly was managed very satisfactorily. I only wish that they were all managed as well.

HENRY T. RICKETTS, M.D., (*Chicago*): We have had a patient who will run a close second to Dr. Peck's, and of a very similar nature with respect to the disturbed home background—a young girl who has been admitted 34 times in acidosis in a period of 10 years to our hospital in Chicago. Each time she would have difficulty with her family, she would refuse to eat, and then, not eating, would also omit her insulin, so that ketosis and acidosis promptly developed. As time went on, she learned that she had to take her insulin whether she ate or not, with the result that on one occasion she came into the hospital in mild acidosis, with a serum CO_2 level of 13 millimols per liter, and a blood sugar of 76 mg. per 100 cc., a perfectly normal glycemic level. This, I would suppose, is a manifestation of the capacity of emotional disturbances to produce ketosis of such a degree as to lead to frank acidosis, and probably also is an expression of the very poor glycogen reserve that this young woman had, with the result that fat metabolism was taking place at a very rapid rate. The only difference between Dr. Peck's case and ours is that we have done a better job of producing vascular lesions, perhaps, than he has. This girl now has frank micro-aneurysms in both retinae.

J.A. SMYTH, M.D., (*Northern Ireland*): In the pursuit of the biggest ever, I don't think Northern Ireland can compete with the United States of America, but we have had a patient who has been admitted 15 times in 5 years, each time in coma, and in investigating this case, it was found quite similarly that home conditions were responsible. She had no psychoneurosis as far as we could make out, and as far as our psychiatric people could advise, but she was living under wretched home conditions where life was miserable, and the bright and pleasant life in the hospital appealed to her, and when she got tired of living under these conditions, she simply stopped her insulin and was brought in in coma. There is no solution to that as yet, as far as we have been concerned, and I don't know whether we could think out something along the lines that Dr. Peck managed.

Another interesting experience occurred very early in the history of insulin, when insulin was frightfully expensive. We had a man who was admitted five times, and each time his recovery from coma cost my hospital between 400 and 500 pounds, and it presently became a problem—what were we going to do about this? Hospital finances were voluntary in those days and it was rather difficult to think of what could be done about it. However, the family practitioner solved the matter for us, because he left this man for about 36 hours in coma in his own house, and when he was brought to the hospital, we couldn't bring him out of the coma and he died.

H. WHITTAKER, M.D., (*London*): I was most interested in this report of Dr. Peck's because, of course, these are the people who, with children, come under residential care in this country, and we often get a history, even in a young child, of a series of five or seven quite severe episodes of ketosis. I am most interested in this question of emotional upset because my own feeling is that there is always something mechanically wrong, that the emotion in some way disturbs the diabetic regime.

When we have the children under residential care, emotional upset often shows itself in an attack of vomiting, and that, I think, is where the diabetes starts to go wrong. If they have a bilious attack when they are in residential care, a urine test is immediately done, and effective treatment started, and so they don't go into these severe episodes of ketosis. When they leave residential care, most of them have grown out of this behavior difficulty, but there still is a very small number —and they usually are diabetics with a rather low intelligence quotient—who will continue to give trouble in this way.

J. J. GROEN, M.D., (*Amsterdam*): We have also had several patients with diabetes in whom we have had to make a diagnosis of psychoneurosis, and very often of obvious psychopathy. Now, lately, we have come to ask ourselves how far we, as doctors, may have been responsible for the production of these abnormal mental states. At least two ways can be visualized in which these abnormal mental states can develop in people who are under medical treatment.

The first is due to the fact that many of these children when they were very young were kept in hospitals for very long periods of time. A girl we have, for instance, who has been admitted 36 times, was kept in a hospital when her diabetes was first discovered, from her third to her seventh year, because this was just about the time when insulin was brought in. She was regimented very rigidly, and she herself ascribes her present attitude toward her disease to this regimentation and imprisonment, as she calls it.

The second way in which, perhaps, we might damage the patient is through too rigid control. Sometimes they may do it themselves. By subjecting them to repeated insulin shocks, it has been demonstrated that severe, persistent hypoglycemia may lead to brain damage, and that brain damage may sometimes show itself

in psychopathic behavior disorders. Our patient went into severe hypoglycemic shocks several times, either because she didn't pay enough attention or because she was too rigidly controlled.

It has to be recognized that the real danger of damaging diabetic patients, especially young ones, can be in irregular control, both by ketosis and sometimes also, by overtreating and damaging their brain, and thereby their emotional life, via repeated severe hypoglycemia.

C. STRIKER, M.D., (*Cincinnati*): I would like to record, inasmuch as this is an experience meeting, one of our successful failures! We experienced a similar situation in an eighteen-year-old diabetic of about ten years standing, who was admitted to the hospital at least twenty times. After much psychiatric supervision and metabolic control, we admitted that we could not control the patient. We then considered the question of a prefrontal lobotomy, and it was performed. That patient now, although a transformed individual, has not been admitted to the hospital in keto-acidosis for at least two and one-half years.

H. H. BERG, M.D., (*Hamburg*): Considering the possible causes for repeated comatose diabetic states, I would ask if others have observed any influence of a seasonal factor. We have seen several cases in which coma occurred on nearly the same date, in autumn, in a sequence of some years.

DR. PECK, SR.: We have not noticed seasonal incidence in this patient of ours. In the period of 1952-53, the patient went through all seasons and had a total of eighteen comas that year.

DR. STRIKER: I apologize for rising again. I would like to ask Dr. Peck—and all of us have had the experience—what is his explanation, if possible, of the apparent mildness of this individual after such severe trauma. One is impressed in the reversion of diabetics from their ketotic state, if the overlay of stress is removed. They almost invariably return to a relatively mild state. But here is an individual who has had many traumatic experiences and one would expect pretty severe changes in endogenous insulin supply if that is a factor. Does Dr. Peck have an explanation for the mildness after her readjustment?

DR. PECK, SR.: By mildness, you mean the insulin requirements? Well, she had been receiving between one and two hundred units for long periods of time. Since the beginning of this year, when her emotional readjustment has been so much better, she has rarely shown any glycosuria at all and has had a continuous reduction in dosage of insulin from 100 down to 60. How much farther she will go, I have no idea. I also have no good explanation of the fall that has occurred thus far. However, I do feel that the insulin requirement per se, as measured in number of units per day, does not reflect absolutely the severity, the real severity, of the diabetic in that occasionally one sees an individual who will tip over into acidosis very promptly on withdrawing a small dose of insulin, 20 or 30 units, and have ketosis within a few hours; whereas in other patients, usually the older, obese type of individual, one may see 100 units withdrawn without much particular change. I would assume that this patient, because she is young and has gone through this period of several years of traumatism, probably has a total lack of circulating insulin of her own.

A Comparison of Obese and Nonobese Diabetic Subjects

Ian Murray, M.D., and Ian Wang, M.B.,† Glasgow*

From the clinical aspect the obese, lipoplethoric diabetic differs in many respects from the nonobese insulin-deficient patient, as has been pointed out by Lawrence.[1] Nevertheless, published statistics with regard to diabetes do not generally take cognizance of such differences, and it appeared that it might be of interest to investigate the characteristics of these two groups separately. Accordingly we undertook a study of 1,000 patients all of whom had been diabetic for at least one year and who were attending the diabetic clinic at the Victoria Infirmary in Glasgow.

METHOD

Before classification according to body weight is possible it is essential to adopt a standard for ideal weight. For this purpose we have used the tables for relative height and weight at different ages according to Lister from the American Medico-Actuarial Mortality Investigation reproduced by Finlayson,[2] accepting as the ideal the average weight of the thirty to thirty-four year age group for this or any older age. For younger patients the average for their age was taken as the ideal.

More elaborate methods have been suggested, particularly that of the Metropolitan Life Insurance Company,[3] which has published tables of ideal weight for women according to the frame of the patient. It is often difficult, however, to assess with any precision whether the patient has a small, medium, or large frame. The present simpler method would appear in general to be adequate, if perhaps somewhat lenient to the obese patient of smaller frame, since the weights we have accepted as ideal fall between the upper ranges given for the medium-framed and the lower ranges for the large-framed, as shown in figure 1.

As might be expected, loss of weight was frequently found to have occurred just before the onset of diabetic symptoms, but in certain cases the patients had maintained a fairly constant weight for many years, although

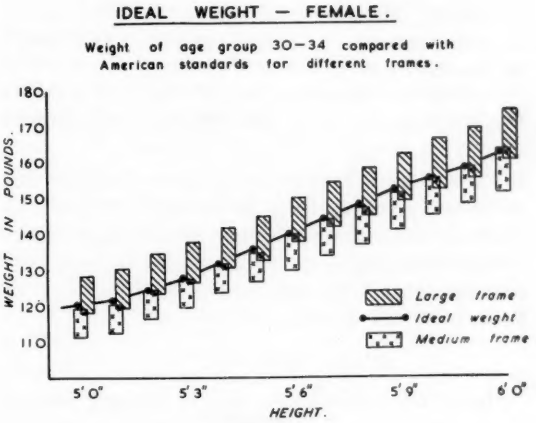

FIGURE 1

at a former age they had been much heavier. It was on account of these differences that it was considered advisable to use for our present purpose the weight of the patients when they became diabetic and not their previous maximal weight.

The obese group (group 1) consisted of all patients who were 20 per cent or more above ideal weight. Those who did not exceed the ideal weight had to be subdivided according to whether they had at no time been heavier than the ideal (group 4) or whether at some earlier age they had exceeded it (group 3). A considerable number were found to be overweight but not to exceed the ideal by 20 per cent at the time diabetes was discovered (although doubtless many had exceeded this limit earlier), and these were classified as group 2. The numbers for each of these four groups are shown in table 1. For the purpose of the present study comparison was made only between those who were still frankly obese when diabetes was detected (group 1) and those who at no time had exceeded the ideal weight (group 4).

There is a possible error in analyzing a series of so-called "old" patients. Since the general experience is that obese patients, for a variety of reasons, are more prone to absent themselves from a diabetic clinic than is the case with the acute thin diabetic, the proportion of obese patients may be smaller than it should in fact be. To check this possibility we examined 300 consecu-

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TABLE 1

Classification of 1,000 patients in present series compared with 300 consecutive new cases

Group	Present Series	New Cases
I. Obese (exceeding 20% overweight).	**337 (33.7%)**	**124 (41.3%)**
II. Intermediate (+5 to +20% overweight).	215 (21.5%)	75 (25.0%)
III. Nonobese but formerly overweight	161 (16.1%)	38 (12.7%)
IV. Nonobese	**287 (28.7%)**	**63 (21.0%)**

tive new patients. The number of these falling into each of the four groups is shown also in table 1, from which it will be seen that the proportion of new obese patients is significantly higher. In the subsequent analysis, however, it has not been considered necessary to make allowance for this difference.

RESULTS

Age of Onset of Diabetes. This is strikingly different in the two groups. In the obese patients 94 per cent were 40 years of age or more when diabetes was detected, whereas almost 52 per cent of the nonobese were under this age at the onset. Moreover, unlike the obese patients, who usually develop the disease between the ages of 50 and 65, the nonobese are distributed very much more evenly in the various decades of life. This is shown in the diagram (figure 2), which in addition gives an indication of the difference in sex ratio.

Sex Ratio. The ratio of males to females in the 1,000 patients examined is 1:2.03, a value approximating very closely that of 1:2.26 found by Munro, Eaton and Glen[4]

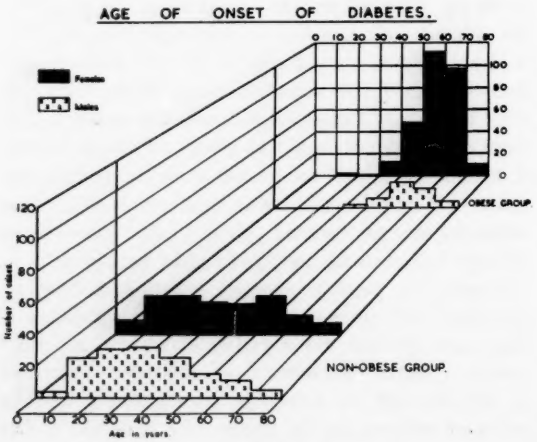

FIGURE 2

in a previous study at our clinic, and identical with the ratio of 1:2.06 obtained from the analysis of deaths from diabetes in Scotland from 1931-1940. When, however, the obese and nonobese groups are examined separately very different values are obtained. For the former the ratio is 1:5.13 and for the nonobese it is 1:0.94.

Insulin Requirements. It is to be expected that there would be a vast difference between the two groups as regards insulin requirements. The great majority (92.0 per cent) of the nonobese patients require insulin, but only a small proportion (17.5 per cent) of the patients in group 1 are having insulin (table 2). Nevertheless, insulin is certainly necessary in a number of the obese group. In this group 49 patients take insulin. In 29 patients dietary restriction alone had proved inadequate. Of these patients, 15 had reduced to ideal weight and in 14 a substantial fall in weight had been effected. All suffered from very considerable hyperglycemia and frequently complained of diabetic symptoms, for the relief of which it seemed necessary to prescribe insulin, although this, in 8 patients, had the undesirable effect of a gain in weight so that they became at least 10 per cent above ideal weight. Of the remaining 20 patients, 8 had already started taking insulin prior to attending this clinic and continued to do so. The other 12 patients showed no reduction in weight despite much encouragement and a lengthy trial of dietary control. These too had to be given insulin for symptomatic relief. Doubtless in many cases the fault lay with the patient's failure to adhere to dietary instructions. Although it may be argued that better cooperation by the patient may have rendered insulin unnecessary, nevertheless in certain cases it is essential, since at least 6 patients in the obese group showed a definite liability to develop diabetic ketosis. It will be seen from table 2 that in both groups there is a greater tendency for this to occur in the female.

Insulin sensitivity as evidenced by hypoglycemic episodes was found in 14 cases.

Inheritance of Diabetes. Both obese and nonobese

TABLE 2

Differences between obese and nonobese diabetics

	Obese (337)		Nonobese (287)	
	Male (55)	Female (282)	Male (148)	Female (139)
Mean age of onset	57.73	56.10	36.01	37.30
Sex ratio	1	5.13	1	0.94
Taking Insulin	11 (20.0%)	48 (17.0%)	137 (92.6%)	127 (91.4%)
History of Ketosis	0	6 (2.1%)	14 (9.5%)	37 (26.6%)

groups have a family history of diabetic relatives in approximately the same proportion—27.3 per cent for the obese and 25.1 per cent for the nonobese. (figure 3).

However, when inquiry was made into the nature of the diabetes in these relatives it was found that there is a definite tendency to inherit the same type of diabetes. In the obese group 17.2 per cent of patients have obese diabetic relatives, as compared with 6.6 per cent in group 4. On the other hand, only 11.9 per cent of obese diabetics have nonobese diabetic relatives, as compared with 19.2 per cent of the nonobese group 4. In general where a family history of diabetes is given, the diabetic relatives are all of one or the other type, either obese or thin, but 6 patients of group 1 and 2 patients of group 4 have relatives of both types. Following this general tendency in inheritance, diabetic siblings are predominantly of the same type as the patient, but in both groups there is a significant proportion of diabetic siblings of the type opposite to that of the patient.

The relative significance of diabetes in the father or the mother was considered. Although our numbers are scarcely sufficient to provide a basis for conclusions, certain tendencies are observed (figure 4). The fact that the mother is an obese diabetic appears of particular significance, and her child, if diabetic, is most commonly of the same type. In the obese group, 6.2 per cent have such a mother, compared to 1.4 per cent in the nonobese group. In both obese and nonobese diabetic patients, very similar proportions gave a history of the mother being a nonobese diabetic—3.3 per cent in group 1 and 3.8 per cent in group 4. With regard to the fathers, our figures are too small in the obese group to be significant, although it is apparent that in this group diabetes in the father is much less common than in the mother. In the nonobese group the proportion of patients having a nonobese diabetic father is virtually the same as the proportion having a diabetic mother of this type. In other words, where the nonobese diabetic has a nonobese diabetic parent this is almost as frequently the father as the mother. An obese diabetic parent is uncommon in this group. It is obvious that a diabetic parent may have offspring developing diabetes of the type opposite to his or her own.

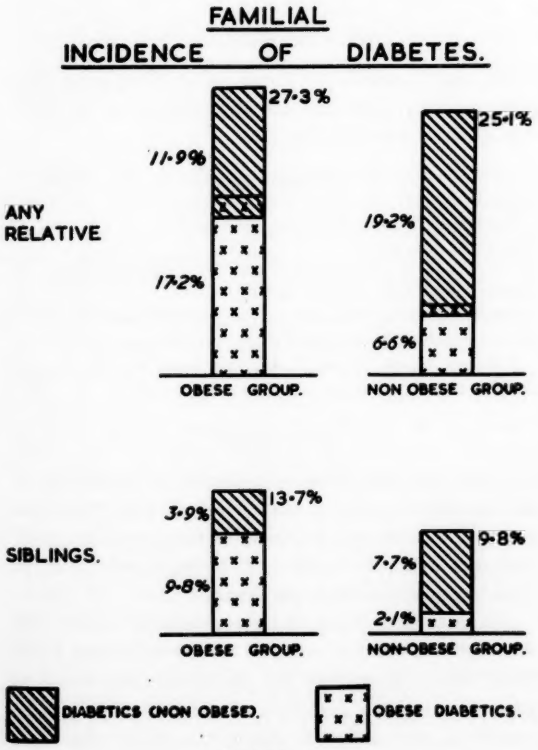

FIGURE 3

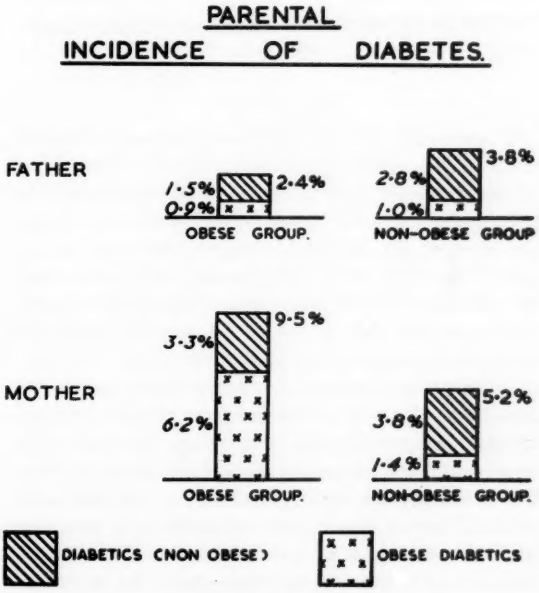

FIGURE 4

Inheritance of Obesity. As is shown in figure 5, the obese group of diabetics has a remarkable family history of obesity, 67.7 per cent of these patients having obese though nondiabetic relatives. In the nonobese group such relatives are possessed by only 23.0 per cent. This figure approximates very closely that of 22 per cent which we found in a control series of nonobese, nondiabetic hospi-

tal outpatients whom we examined.

It is worthy of note that in the obese group the incidence of obesity in all branches of the family, male and female, is much higher than in the other group and cannot be related solely to pregnancies as has been suggested.

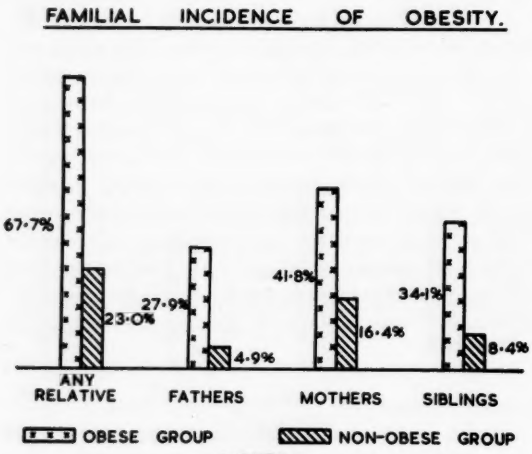

FIGURE 5

CONCLUSIONS

It is apparent that there are many differences between obese and nonobese diabetics. It seems probable that statistical surveys of diabetics as a whole may not be truly representative of either type individually; witness, for example, the difference in sex ratio between the two groups. It would be of great interest if diabetes could be classified into different types which could be dealt with separately, but it has to be admitted that such classification presents many difficulties.

In the present series of 1,000 cases nearly 40 per cent have been regarded as intermediate between the two typical groups. Even these two groups show a certain intermingling. For example, some obese diabetic patients may eventually develop characteristics of the more acute nonobese group. Again this intermingling is seen in a study of inheritance of the disease. An obese diabetic mother may have a child of either type. An acute nonobese diabetic may have an obese mildly diabetic sibling. Nevertheless, these difficulties should not obscure the fact that important differences do exist between different types of diabetics, the further study of which may elucidate some of the problems of diabetes.

CONCLUSIONES

Un Comparation de Obese e Nonobese Diabeticos

Il ha multe evidente differentias inter obese e nonobese diabeticos. Il es probabile que le statistica del diabeticos in general non provide un ver representation del duo typos individual. Iste observation es supportate per exemplo per le facto que le statistica monstra pro le duo gruppos un differentia del proportion inter le sexos. Il esserea de grande interesse si le population diabetic poteva esser classificate in varie typos con que on poterea occupar se separatemente, sed on debe admitter que un tal classification presenta multe difficultates.

In le presente serie de 1000 casos, circa 40 pro cento esseva considerate como intermediari inter le duo gruppos typic. E etiam le gruppos mesme monstra un certe intermiscimento. Per exemplo, certe diabeticos obese disveloppa in le curso del tempore characteristicas del plus acute gruppo nonobese. Tal intermiscimento es observabile etiam in le studio del hereditabilitate del morbo. Un obese matre diabetic pote haber un infante del un e del altere typo. Un nonobese diabetico acute pote haber un fraterno qui es un diabetico levemente obese. Nonobstante, iste difficultates non deberea obscurar le facto que importante differentias existe inter differente typos de diabeticos. Le continue studio de iste differentias va possibilemente contribuer al elucidation de certe problemas de diabete.

ACKNOWLEDGMENT

We wish to express our appreciation of the great help given to us by Miss Elizabeth M. Irving in the compilation of the statistical data.

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DISCUSSIONS

CECIL STRIKER, M.D., (*Cincinnati*): I would like to ask Dr. Murray, in the obese children from the obese parents, whether psychological factors were involved? Did they want their children to be fat, or what was the dietary pattern of those children?

DR. MURRAY: I am afraid I could not answer that, although I do believe there is a very important factor there. Not, I think, that the parents admire obesity in their offspring, but that their environment does play an enormous part and that obesity, in many cases, is a reflection of psychological upset.

Level of Plasma Amino Acids in Eviscerate Rats Given Glucose and Fructose with and without Insulin

Dwight J. Ingle, Ph.D., Violeta Flores, B.S., and Gloria Torralba, B.S., Chicago*

This is one of a series of studies on the effect of hormones upon protein metabolism in the eviscerate rat. Insulin causes a temporary decrease in the level of plasma amino acids (PAA) in the eviscerate rat and suppresses the rate of increase in PAA.[1] How do this and other effects of insulin upon protein metabolism relate to the action of insulin upon carbohydrate utilization? If the changes in protein metabolism are secondary to a primary action of insulin upon the utilization of carbohydrate it should be possible to suppress the rise in PAA in the eviscerate rat by enhancing the utilization of carbohydrate by other means. There is some evidence that fructose is well utilized in the absence of insulin, and it is commonly believed that insulin does not affect the utilization of fructose. In the present experiments we have tested the hypothesis that fructose might suppress the rise in PAA following evisceration. The results are negative.

METHODS

Male rats of the Sprague-Dawley strain weighing 250 ± 5 gm. were fed Rockland rat diet. Nonfasted rats were anesthetized (intraperitoneal injection of 18 mg. of cyclopentenyl[1]-allylbarbituric acid sodium) and functionally eviscerated by the technic of Russell,[2] the gut being removed, but the liver remaining *in situ* after its arterial and portal vessels were ligated. The kidneys and adrenal glands remained intact. Continuous intravenous infusions of solutions of glucose or fructose with or without regular insulin (Lilly) were made by the method of Ingle, Prestrud and Nezamis.[3] The fluid was delivered into the saphenous vein of the right hind leg at the rate of 20 ml. per 24 hours per rat. Six rats were infused at a time so that rats receiving glucose and rats receiving fructose were compared simultaneously. All infusions were for a period of three hours beginning immediately following evisceration.

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This work was supported by grants from the American Cancer Society as recommended by the Committee on Growth and from the United States Public Health Service.

At the end of the infusion period the blood was drained from the abdominal aorta by cannula. Heparin was used as an anticoagulant. The level of plasma amino acids (PAA) was determined by the method of Hamilton and Van Slyke[4] and the level of reducing substances in whole blood by the blood glucose method of Miller and Van Slyke.[5]

RESULTS

The conditions of the experiments and data are summarized in table 1. The level of PAA was affected by insulin and was not significantly changed when fructose was substituted for glucose. Insulin suppressed the level of reducing substances in blood under all of the conditions studied here.

DISCUSSION

In the absence of insulin the values for reducing substances in blood were lower when fructose was administered than when an equal load of glucose was given. In the presence of insulin the level of reducing substances in blood was depressed to a lower level when glucose was given than when an equal load of fructose was given. Since a method specific for fructose was not used, it is not possible to know the extent to which the changes in levels of reducing substances represent exogenous fructose or endogenous glucose. It seems probable that fructose is better tolerated by the eviscerate rat without insulin than is glucose, and that insulin has a smaller effect upon fructose tolerance than upon glucose tolerance.

The effect of insulin upon the level of the reducing sugars of blood was striking in eviscerate rats given either glucose or fructose, but this does not prove that insulin affected the metabolism of fructose. The apparent effect in the rats given fructose may have been due solely to accelerated disappearance of the endogenous glucose present in the extracellular fluids at the time of evisceration.

It is clear that the administration of fructose without insulin to the eviscerate rat does not suppress the rise in PAA, although greater amounts of reducing sugars

TABLE 1

Level of Plasma Amino Acids (PAA) and Reducing Substances (RS) of Whole Blood Three Hours Following Evisceration Averages and Standard Errors

Carbohydrate* load mg./100/h	units insulin 24 hrs.	glucose			fructose		
		N rats	RS	PAA	N rats	RS	PAA
16	0	16	190± 6.58	8.56±0.27	16	137± 9.45	8.45±0.14
25	0	9	209±16.02	7.72±0.26	9	187±13.1	8.17±0.26
25	16	9	40± 4.41	2.93±0.86	9	65± 4.83	3.01±0.19
40	0	9	306±13.8	7.16±0.44	9	220± 3.28	7.54±0.32
40	16	9	55± 4.21	3.12±0.11	9	87± 3.13	2.95±0.07
60	0	9	416± 8.12	8.51±0.27	9	268± 4.20	8.00±0.29
60	16	9	85± 9.52	3.39±0.12	9	146± 6.60	3.09±0.15

*The carbohydrate load is expressed as milligrams per 100 gm. of rat per hour.

disappear from the blood than when glucose without insulin is given. In other experiments[6, 3] we have shown that acceleration of glucose utilization by muscle work does not simulate the action of insulin upon PAA, nor is the rise in PAA affected by glucose load even in the absence of insulin.[7]

SUMMARY

Insulin suppresses the rise of plasma amino acids in the eviscerate rat. One hypothesis as to how the effects of insulin upon the metabolism of carbohydrate and protein are related holds that insulin stimulates the utilization of carbohydrate to meet energy requirements, thereby averting the need to catabolize protein, and also supplies the energy needed for protein synthesis.

It has been claimed that fructose is better utilized than glucose in the absence of insulin. The possibility that fructose would substitute for insulin in suppressing the rise in plasma amino acids was tested in the present experiments. Functionally eviscerated rats were given continuous intravenous infusions of either glucose or fructose with and without insulin for a period of three hours. The level of plasma amino acids was suppressed by insulin, but was not significantly changed when fructose was substituted for glucose.

SUMMARIO IN INTERLINGUA

Le Nivello del Amino-Acidos Plasmatic in Rattos Eviscerate, Recipiente Glucosa e Fructosa con e sin Insulina

Insulina supprime le augmento de amino-acidos plasmatic in rattos eviscerate. Un del hypotheses in re le interrelation del effectos de insulina super le metabolismo de hydratos de carbon e super le metabolismo de proteina stipula que insulina stimula le utilisation de hydrato de carbon in responsa al requirimentos de energia e assi evita le necessitate de catabolisar proteina e in plus provide le energia requirite pro le synthese de proteina.

Il ha essite asserite que fructosa es melio utilisate que glucosa in le absentia de insulina. Le possibilitate que fructosa pote ager como substituto de insulina in supprimer le elevation del amino-acidos plasmatic esseva investigate per le experimentos hic reportate. Functionalmente eviscerate rattos recipeva continue infusiones intravenose de glucosa o de fructosa con e sin insulina pro un periodo de tres horas. Le nivello del amino-acidos plasmatic esseva supprimite per insulina sed non esseva significativemente alterate quando fructosa esseva substituite pro glucosa.

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What I Teach My Diabetic Patients

Panel Discussion

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Moderator

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Boston

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MODERATOR PRISCILLA WHITE: It is obvious that, without new therapeutic discoveries, the better prognosis for the diabetic patient today depends upon his greater self-knowledge of this disorder. Therefore, the subject of our panel concerns the teaching of diabetic patients.

The panel members, coming as they do from all sections of the country, should give us the teaching goals of the entire United States. Their qualifications are well known to this audience. The teaching experience of this panel exceeds two centuries. From these experts, we should learn the subjects and the technics which they have found to be successful in maintaining their diabetic patients in the most nearly normal state. Beginning with our problems, as we meet them in the patients, let us question our panel.

Dr. Rippy, how do you indoctrinate the new diabetic, especially the adult, shocked with the diagnosis of a chronic disorder?

Presented at the Fifteenth Annual Meeting of the American Diabetes Association in Atlantic City, June 5, 1955.

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With your insight, how do you handle this problem?

DR. EDWIN L. RIPPY: At the onset, one might analyze the physician who is assuming the responsibility for this diabetic patient. What is his attitude?

There are five things which I think are absolutely necessary:

1. The physician must be well grounded in the fundamental concepts of good diabetic care. 2. He must believe in them firmly and definitely. 3. He should be tempermentally adaptable to the long-term relationship with his patients. 4. He should be able to develop technics of teaching. 5. He should have the patience to accept the perverse and obstinate personality of the diabetic.

If after this soul searching he finds himself with these qualifications, he is likely to be acceptable as the physician for the diabetic patient.

I wish I could remember the author of a simple little story to give him credit for it. It is the story of the middle-aged matron whose diabetes had just been diagnosed and who had been referred to a physician who specialized in this disorder. Very hopefully, she said to him, "I understand you specialize in the treatment of diabetes." He said, "Madam, I am afraid you have been misinformed; I do not do so." She was quite taken aback. But he added, "I simply specialize in teaching patients how to treat their own diabetes"—a very important moral.

Often, in talking with new diabetic patients I eventually reach the point where I ask, "There are several things you must learn. Do you know what they are?" Immediately, they answer, "Yes, two of them, diet and

insulin." Then I reply, "Not first. Even more important than the regulation of diet and of insulin is the adjustment of your attitude. If I teach you about changing diet and insulin before I teach you to adjust your own attitude, it is just like giving you a high-powered automobile and putting you on the road without teaching you how to run it."

I think every good doctor has to be a bit of a showman. He must develop technics. There is no substitute for the long-term personalized relationship with the individual patient. One must become part of his life and must develop, in the beginning, trust and mutual confidence.

Although the story of diabetes, to me, is one of hope and promise, I am rather convinced that it is a bit of a mistake to teach the diabetic, at the onset, that he can live as usual. I have gotten away from that, because I think that creates a misconception.

I am a Baptist, and Dr. Joslin has taught me, without knowing it, that every man who takes care of diabetics must be an Evangelist! I do not think we should talk about complications as the Baptist minister would, but I think the patient should know the consequences of poor control.

I use three terms in talking to patients. I tell them, "I can give you three types of control. The first is symptomatic control—easy to do. I can give you a little insulin, and all of your symptoms will vanish. But that will not do the job for long. Or I can give you *survival* control; I can teach you just a little more, and you can do more. You can survive; but inevitably, you will probably develop the so-called precocious senility with loss of sight or limb. Therefore I would like to teach you what I call protective control; that is the real thing."

I also think the diabetic should be given hope and promise and should familiarize himself with the therapeutic progress of the last few years. I think he should be told that within his lifetime, particularly if he is within the younger decades, there will probably be great advances in the field of diabetic care. Who knows? Simpler methods of control, perhaps prevention and hope for cure.

In other words, the friendship with the patient, the facts, the promise, and the hope.

MODERATOR WHITE: Thank you, Dr. Rippy. What a fine start for your patients!

I think all members of the panel treat diabetic children. Dr. Guest, you treat diabetic children exclusively, so won't you tell us how you develop a healthy attitude in the child, and what is much more difficult, a healthy attitude in parents toward the child's diabetes?

DR. GEORGE M. GUEST: Thank you, Dr. White.

As Dr. White says, my experience is more limited than that of my colleagues, i.e., limited to an age period under 15 or 16 years.

Juvenile diabetes is relatively uncommon compared with the adult diabetic population. But it has an importance far out of proportion to its incidence because it requires a daily routine of self-management and because the diabetic child has much longer to live with this disease than the adult who develops it at 60 or so.

The indoctrination, as Dr. Rippy so ably stated, must be directed to developing a healthy attitude toward the disease, to help the child accept and live with it with minimal worry. I say to the child and to the parents that diabetes is an admitted nuisance. Of course, it is a nuisance to take insulin each day and to test the urine in order to regulate the insulin dosage. But, beyond that admitted nuisance, it must never be regarded as a handicap. The child is to engage in all of the activities of his nondiabetic friends. We teach the parents that they must not forbid games or activities for reasons related to diabetes and must avoid implications of invalidism.

The instructions to the parents and to the children should be simplified as far as possible but, of course, should not be oversimplified with sacrifice of necessary knowledge. In our clinic, I have aimed at simplification of instructions for both parents and the children, and the instructions which they read and follow are reduced to these four and one-half mimeographed pages. (See appendix in Holt and McIntosh *Pediatrics.*) Some diabetics will read a whole book but, in our clinic group, not many of them will. If we can reduce instruction to a minimum, it is desirable.

The desiderata for the diabetic child is to sustain good health, normal growth and development. One can limit diet in an adult, and, to avoid obesity in some, that is desirable. But you cannot limit food intake below normal requirements without handicapping growth in a child. Whatever the dietary regimen, the important point is that adequate insulin must be given at all times. The parents and the children themselves must practice eternal vigilance to adjust the daily dose of insulin as needed. They must accept the precept that acidosis or coma should never occur. They must be alert to the necessity of taking extra insulin during acute infections and of never carelessly omitting insulin. If they are alert in making their tests, especially for acetone, they possess the most important means of detecting impending ketoacidosis, and in the presence of glycosuria the most important sign indicating the necessity for more insulin.

In developing a healthy attitude toward the disease, I might tell a little story, something which happened in our clinic recently. An eight-year-old girl, who had

been diabetic since the age of eighteen months, had always accepted the diabetic routine without complaint. Suddenly, when she was in school, her mother said, "Dr. Guest, I think Sally, for the first time, seems to worry about being diabetic. I want you to talk to her." I did. I went through the usual discussion of what it meant; it was an admitted nuisance and so on. She listened to this for a while; then she said, "Well, I would rather have what I have than what Mary Jones has." I quickly gathered that this was a neighbor friend. I said, "What is the matter with Mary Jones?" Her reply was, "She has asthma and has it bad!" (Laughter)

MODERATOR WHITE: Thank you, Dr. Guest.

Dr. Holcomb, you have developed so many interesting technics in teaching, and you are so meticulous about diet instruction, won't you start the discussion of those two subjects, technics of teaching and diet instruction?

DR. BLAIR HOLCOMB: When we see a new patient who has developed diabetes recently, we hasten to tell him that he is going to live a long time with diabetes provided he controls it. The objectives for which he should aim are a comfortable, useful, and long life, and no diabetic achieves those objectives unless he is trained intensively and extensively.

Perhaps we have put more emphasis on the training of the patient than some people think is necessary. I have never seen patients who knew too much about taking care of themselves, and I would like to tell you in detail how we teach them.

We hold classes every morning from 9 to 11, every other afternoon between 2 and 3. Our morning classes are taught by a young woman who was selected because she understands how to deal with people. We have taught her what we want *her* to teach the patients. We believe that the over-all education of the patients should not be put in the hands of a dietitian but should be kept in the hands of the practicing physicians. We do not believe in physicians turning the education of the patients over to interns or residents. We think a physician rightly should take enough time to talk to his diabetic patients, not only individually but also in groups.

Our patients, both in and out of the hospital, meet between two and three o'clock Monday, Wednesday and Friday. As much as possible, our in-patients are in ambulatory units such as Dr. Joslin will describe. There is an esprit de corps which is accomplished by this grouping of diabetic patients. One never can achieve as much with patients isolated in different parts of the hospital. Our patients exercise together; they go to classes together; they walk to the diabetic dining room and eat together. It all becomes a social event. They teach each other; you cannot stop them from doing it. It helps the new patient who has been hospitalized for two days to take over voluntarily the instruction of the patient who has been admitted today.

I want to emphasize some things which I know Dr. Frederick Allen will subscribe to. I had a letter from Dr. Sherrill shortly before he died last year, in which he was bemoaning the fact that diabetic control today is not what it should be. I wish to emphasize the fact that we need a renaissance in the importance of diet. The diabetic is living on a subsidy, as it were, the subsidy being insulin; and, like industries and people who endure because of subsidies, the diabetic many times does as little as possible to maintain good control.

Another technic of training includes continued education through the years. It is fine to educate a patient intensively over a ten-day or two-week period, but it is still more important to keep that patient educated. For this reason, in 1928 I devised an informal diabetic bulletin. I never realized, when I started it as a monthly bulletin, that I was assuming a job which I still have. In this bulletin we try to keep the patient educated, tell him about new things which are proved and are good; we try to build and sustain morale. It has been a very valuable means, I think, of achieving long-time control; and I believe in long-time control.

In summary, I want to say one thing more, Dr. White, and that is this. We teach 87 per cent of our patients to calculate a diet. We do not use exchange diets. I have a suspicion—it is almost a conviction—that the popularity of exchange diets is due to a single fact, namely, that many physicians today do not themselves know food values. They do not even know how to calculate a diet. Therefore, they take the easy way out.

When you treat people with a lifetime problem, you must build discipline and attempt to build character from the start. You do not do it with loose dietetic control.

MODERATOR WHITE: Thank you, Dr. Holcomb.

I would like to ask Dr. Guest about technics which the pediatricians have developed. Most of us, in relation to diabetic diets, think in terms of two diets, the diabetic diet and the nondiabetic diet.

But the pediatricians have three diets: Diabetic diets which they do not prescribe; nondiabetic diets which they do not prescribe; and the normal diet which they do prescribe. When I quiz their children about this, their diet is what I call an excellent diabetic diet. I think this is wonderful technic. I am not being facetious; it is particularly important for diabetic children.

However, instead of asking you about that, Dr. Guest, since you are the chemist of our group, will you discuss briefly the technics for teaching various kinds of tests?

DR. GUEST: Dr. White, your first remarks were about

the normal diet. (Laughter)

I would like you to recall my regimen employing the normal diet. The best example of all was the nine-day-old baby who was breast-fed for 10 months. That baby is now eight and one-half years old and living by taking what we call a normal diet; the instructions regarding the diet were the same as those given for nondiabetic children *but better*. As most of you know, I follow what Dr. Holcomb will call loose dietary practices. Children eat largely because of appetite. They spill some sugar most of the time. They can sustain good health and can avoid the acute accidents of acidosis if they are never allowed to show ketonuria. My children are taught to avoid excessive ketonuria, and that means testing for acetone frequently.

Fortunately, new tests are remarkably helpful and simple. Either the Clinitest or the Galatest are accurate and much easier to use than the Benedict test. Some people prefer the Benedict solution still, but for the mother who is sending her child off to school in the morning, these simple tests are invaluable.

Both the Clinitest and Galatest are sensitive. There is a new test for sugar which was mentioned this morning, employing the specific glucose oxidase. This promises to be the simplest of all. If it is distributed as promised during the year, it is going to be remarkably convenient for all of our children and older diabetics.

I would like to say another thing about the testing. I try to teach diabetic children to conduct their own diabetes detection drive, suggesting that they periodically get urine samples from the members of their families and relatives after a big Sunday dinner or at some such convenient time and do their own relatives' tests. They will frequently diagnose a diabetic in their family and, as the years go on, they will find more.

DR. WHITE: Do you think patients should learn to do their own blood sugars? (Laughter)

DR. GUEST: I think that is to be hoped for. If this new blood sugar test reported in the morning program proves what was suggested, it may be possible for patients to test drops of blood drawn by skin puncture.

MODERATOR WHITE: In contrast to diet, where there is not so much patient prejudice, we all know that diabetic patients are prejudiced against insulin therapy. This must be broken down. As part of their psychological rejection they make many bizarre mistakes.

We must warn patients against these. They must be taught methods for sterilization, regulation, and the signs, symptoms and treatment of insulin reactions.

Dr. Gates, you have talked so helpfully about these problems, won't you start the discussion of teaching insulin therapy to patients with diabetes?

DR. EDWIN GATES: In the first place, I do not think one can succeed in teaching about insulin unless one gains the patients' confidence. It takes time. They must be allowed to ask questions. One cannot hurry; one cannot do all the teaching at the first visit.

I tell patients everything about insulin which may be of use to them. I tell them when it was discovered, in 1921, and something of the history of the discovery and of the miraculous change it created, that diabetics who would have died formerly live now, and that if they follow our instructions they may live as long as or longer than their nondiabetic neighbors.

I explain the various strengths of insulin to them. Errors arise when the pharmacist accidentally sells them unaccustomed strengths. Actually, this error is the patient's because he should check and find out what type of insulin and what strength he is purchasing. Accurate measurement is stressed. I think it is very important that they take an exact amount of insulin. In childhood, failure to be accurate may spell disaster.

I furnish the patient with an insulin syringe approved by the American Diabetes Association. I teach the patient never to get a syringe that can be used for two strengths of insulin. Occasionally I ask them to bring in their syringe for me to see. It is surprising to find that sometimes the patient is not using an insulin syringe. I emphasize that a U-40 syringe must be used with U-40 insulin. Ask your patients to bring in their insulin bottle once in a while. You will find occasionally that they have the wrong insulin. I advise that each diabetic have two syringes in case one breaks.

I teach my patients the proper care of their syringes and needles and make this as simple as possible. Boiling once a week is recommended, and the rest of the time the syringe and needle are kept in alcohol. I stress the importance of getting all of the alcohol out of the syringe because if this is not done local irritation at site of injection may occur.

I emphasize the importance of varying the site of the insulin injection. Most of our patients take their insulin in the thighs in two parallel lines, each injection about one inch apart so that insulin will not be repeated in one area for four weeks. I explain to the patient that repeated injections of insulin in the same place may lead to insulin atrophy.

Instructions are given to keep the bottle of insulin in use outside of the refrigerator. The loss of strength is so slow that it is not important. An extra bottle of insulin should always be kept in the refrigerator.

I place great emphasis on the fact that the patient must never discontinue his insulin without the physician's permission. This must be emphasized again and again

because it happens too often.

I also teach our more intelligent patients how to take insulin every three or four hours at home, according to their urinary sugar. This is only to be done when they have some minor infection and only with the advice of the physician. Using such rules, I have found it is not necessary to hospitalize all diabetics who show sugar and acetone when they have a minor illness.

The final point I would like to make is, that after one has taught patients all of this and much more, as one of the panelists has already mentioned, one must teach them all over again often later in that same year. One must repeat instructions because patients soon forget and disaster results.

MODERATOR WHITE: Thank you, Dr. Gates.

There are some questions I would like to ask members of the panel to answer individually and briefly.

I think all of us who lecture to lay groups are asked these two questions: What happens to the brain in an insulin reaction? Can diabetic patients die in insulin reactions?

Second, what does each one of you tell your patients about complications and, finally, the hope for the curability of diabetes? Dr. Holcomb, will you start?

DR. HOLCOMB: I was hoping you would ask me something else. I want to continue, however, Dr. White. I have to catch a train and I must leave in five minutes.

I said that we would teach 87 per cent of our patients to calculate diets; 13 per cent cannot be trained because they do not have enough education. But, of the 13 per cent, all but one-fourth of them are sent home with someone else trained adequately, leaving the one-fourth who have to use fixed diets. (I do not call these exchange diets.) We train grandchildren; we train the children of the older patients who are not able to be trained in classes.

I want to say a word about office education. If I had one patient with diabetes I would teach that patient whenever I had a chance to do so and if he remained still long enough. Soon, I would have two patients and you know what happens. Presently, you are known among the public and your colleagues as someone who will take time with patients, who will be interested in them, who will continue to be interested in them. This lifetime responsibility for the diabetic patient is really something to give each one of us the feeling of adequacy. It is a lifetime job.

As far as telling people about the dangers of brain damage and overemphasizing death from hypoglycemia, I simply tell patients this: "If you stay on your diet, if you know what you are doing, if you take your insulin properly, if you prevent insulin reactions by taking extra carbohydrate before the effect of additional physical activity has been felt, you do not need to worry about insulin reactions which will cause brain damage."

What was the other question, Dr. White?

MODERATOR WHITE: Complications and curability.

DR. HOLCOMB: What about complications? I tell patients this. We like to imitate the normal as closely as possible in our diabetic patients, and normal people do not get degenerative vascular lesions at a young age. Therefore, we know nothing else to do except to say: "Control your diabetes to the best of your ability; then, the chances of your getting complications will be greatly minimized."

DR. RIPPY: I think you can see that most of the panelists have different types of practice. Mine is an individual practice in an office. I am beginning to find that I like to control my diabetic patients as ambulatory office patients more often than not.

We have devised a little trick in the office and are using it in the hospitals now. It is a formal diet, a little slip on which we obligate the doctor to write the formula for the diet and to do one more thing which is all too often neglected, to put down how he wishes to have the three formal meals distributed and whether he wishes snacks. We indicate below, for his convenience, what we consider to be a snack. I think that if we can teach our doctors to distribute diets to fit the insulin used, insulin reactions can be minimized.

I have read about the sequelae of profound hypoglycemia. I must admit that I have seen it in one instance only, a child. I think we should avoid reactions because they are embarrassing or because they are disconcerting, but I doubt if we should mention too often the fear of brain damage and so forth. I am not too convinced that it happens often enough to be of great consequence.

As to complications, I think, as I said once before, I like to tell people that, "with this disorder you can live almost as long as you want to; you make your own choice. I am going to show you how to do it well. I will teach you the disciplines and then it is up to you. With my help you can live almost as long as you want to. If you live long enough, you may develop some complications. Put them off as long as you can because it is remarkable how many diabetics live normal, productive lives with all the complications they have."

I said before that they should know the penalty of poor control, but, again, I do not think we should emphasize it to the point of producing chronic anxiety.

MODERATOR WHITE: Our time is short. Thank you, Dr. Rippy.

Dr. Joslin, with your experience with more than 40,000 diabetics, won't you tell us about your new plan

for teaching diabetics?

DR. ELLIOTT P. JOSLIN: Before speaking about the plans for the Hospital Teaching Clinic, Dr. White, let us imagine for a moment that this audience is made up of diabetics and relatives of diabetics. What would I want to say to them first? You know, I would enjoy telling them that I am flying home tomorrow afternoon to go to an afternoon tea in honor of Mrs. John Dow who is celebrating her one hundredth birthday. Mrs. Dow is my oldest diabetic and has lived twice as long with her diabetes as she was expected to live without it when she first developed it.

Then, I would call the attention of this audience to the Quarter Century Victory Medal diabetics we now have who are perfect at the end of their 25 years of the disease, with certification from recognized ophthalmologists that they show no trouble in the eyes and from roentgenologists that there is no calcification in their arteries. In 1948, we had only one such, but now we have 58. I would like to add for the benefit of those here as well as for patients in my classes, that the reason for the excellent condition of these individuals is that they controlled their diabetes very, very carefully at the start.

All sorts of patients attend our classes and their mere presence counts far more than words. If a patient is led in blind, no remarks are necessary, although occasionally such a patient will wish to give advice to others. One can take advantage, however, of such methods of instruction which count far more than what a doctor would say. This last week I had two patients who were brothers. One of them controlled his diabetes well for 20 years and the other did not. They stood up there, and the one who had controlled his diabetes well obviously was far more free from complications than the other and the two brothers were willing to give the reason why. That did more good than anything else I said that day.

In general, the diabetic should be looked upon as belonging to a rather superior class. One can take for granted that they will heed advice against marrying another diabetic. Similarly, one can depend upon their love of their family to help to detect others who are potential or possible diabetics in their family, on the grounds that no one is more interested in their own family than are they. I like to put responsibility upon them, not only for protecting their descendants and for detecting diabetics in their family, but also for protecting others. They have for example a responsibility in driving automobiles.

The Agent of the Registrar of Motor Vehicles came to our diabetic class recently. I told him he could talk to the patients for 5 minutes, but they were so interested in what he said that they kept him for 30 minutes. Among other things, he told them that when they applied for a license if they did not put down the fact that they had diabetes they were liable to prosecution for perjury and a fine of $200. Furthermore, if they had an accident and it was known by the insurance company that they had not disclosed to the Registrar that they had diabetes, it was quite likely that the insurance company would refuse to accept responsibility and their home and their savings for a lifetime might be wiped right out.

The patients questioned him and he acknowledged that he did not know how many of those driving automobiles were diabetics or what their percentage of accidents was compared with nondiabetics. Of course, I remarked that my patients probably had fewer accidents than nondiabetics because they lived more carefully.

It certainly was worth while to bring up the question of safe driving in a way that the patients would realize the responsibility they had.

Then, too, I like to put upon the patients the responsibility for research. It is their diabetes and if they want better treatment and more discoveries, it is for them to provide for it. This they are more ready to do than is often thought. Within a few weeks I came into the classroom with a paper bag which Barbara gave me. Obviously it was a heavy bag and, when I opened it, there were 300 pennies, a penny for nearly every day in the year except Sundays and holidays. Think of it—there are two million diabetics in the country. If each would save a penny a day, think of the funds which would be available for research.

For our patients to be in good health after twenty years of diabetes they must have the opportunity for good treatment. That is why we are building the Hospital Teaching Clinic with the idea that we can bring back the younger and more hopeful diabetics who have a long future before them and at lessened expense tell them how they can care for themselves. These younger patients need encouragement and reiteration of treatment. In the Hospital Teaching Clinic they can save money because they will be ambulatory and will require far less nursing service. It is our hope that we can demonstrate the usefulness of this building to such an extent that hospitals all over the world will set aside a few beds to meet similar needs for the younger diabetics who need to be taught and urged and helped how to control the disease.

MODERATOR WHITE: Thank you, Dr. Joslin, and I thank all of you panel members for your interesting and important discussions, and thank you, audience, for staying with us. (Applause)

EDITORIALS

THE JOURNAL DIABETES *IN RETROSPECT AND PROSPECT*

In an editorial entitled "DIABETES Looks Ahead" in the first issue of the Journal, the writer discussed the objectives of the publication. These were defined as fulfillment of the aims of the American Diabetes Association in respect to the dissemination of knowledge of diabetes, the promotion and maintenance of high standards of treatment, and the stimulation of investigation. It was planned that the contents of DIABETES would include material appealing to the widely-varying interests of the Association members and other subscribers including internists and specialists in various other fields of medicine, general practitioners and scientists. That these aims have been achieved with a substantial degree of success has been confirmed by the results of the "Reader Interest Survey" presented in the November-December issue.

The favorable comments received from the majority of readers have been appreciated by the Editors and Editorial Board. At the same time, it is realized that consideration must be given to the possibilities of improvement, to which attention has been directed. Readers can be assured that efforts to bring about continuing progress will be made by the new Editor and his Associate.

The major factor in the success of any scientific publication is the quality of the papers which it can present to its readers. Much of the material published in the Journal has been derived from the program of the Annual Meeting of the Association, and to some extent also, from the Postgraduate Course which has been presented each year since 1953. These programs are planned and organized by committees which thus render indirectly an important service to the Journal supplementing the Editorial Board in the procurement and selection of papers.

Unsolicited manuscripts are submitted to DIABETES in increasing numbers, but more papers written especially for the Journal are desired. Contributions are welcomed from any source in which reliable observations can be made and sound ideas can be developed, whether in a university, a large medical center, or a small town, in the United States and Canada or elsewhere in the world. Each paper has been, and will be evaluated on its own merits. The Editors have available the advice of Board members possessing diversified interests and experience. No paper is arbitrarily rejected on the basis of a single adverse opinion, so that personal bias or disinterest can be eliminated as a factor in selection. Laboratory investigators and clinicians working in the field of diabetes can find that, in this Journal, their reports will come to the attention of the greatest number of readers whose dominant interest is concerned with this disorder and related endocrine and metabolic problems.

FRANK N. ALLAN, M.D., *Vice-Chairman*
Editorial Board, DIABETES

THE EDITORSHIP OF DIABETES

With this issue the Editorship of DIABETES passes from Frank N. Allan of Boston to William C. Stadie of Philadelphia, with Irving Graef of New York as Associate Editor. Dr. Graef will serve as Acting Editor until Dr. Stadie can assume full responsibility for his position in July 1956.

Dr. Allan's long service to the American Diabetes Association has earned him the gratitude and respect of its members, particularly of those who have worked closely with him. He had already proved himself a faithful worker and an able leader when in 1951, having been elected President of the Association, he consented to becoming as well the first Editor of its Journal. Either office would have taxed the energies of an ordinary man. Dr. Allan effectively and cheerfully filled both of them. Continuing as Editor after his presidency, he nurtured the new Journal not only with skill but also with a rare devotion born of love for his work and, more than a little, of a New England conscience with Canadian origins. This has been Dr. Allan's Journal, although he would be quick to deny it, and its manifest success is the success he has given it.

The Journal is extremely fortunate in its incoming Editors. Dr. Stadie's interest in the biochemical aspects

of diabetes, revealed by his many distinguished contributions, will be ideally complemented by Dr. Graef's background in pathology and his present activities in clinical medicine. This is a powerful team, and we have every confidence that under their leadership the Journal will continue to grow and prosper.

HENRY T. RICKETTS, M.D., *President*
American Diabetes Association

ORAL ANTIDIABETIC SULFONAMIDES

In October 1955 three reports in the *Deutsche Medizinische Wochenschrift*[1-3] described a new sulfonamide derivative possessing the ability when given by mouth to reduce normal blood sugar values to subnormal, and elevated blood and urine sugar values in diabetes to normal. Reduction of normoglycemia had been shown with other sulfonamide derivatives as early as 1942,[4-8] but the application to therapy in diabetes mellitus was not made. The earlier compounds were p-amino-sulphonamido-alkyl-thiodiazoles: The current ones are aryl sulfonylureas. Those now under the most intensive investigation are N_1-sulfanilyl-N_2-n-butylcarbamide (BZ 55) and N_1-p-tolylsulfonyl-N_2-n-butylurea (U 2043 or D 860). More clinical evidence is available concerning the former than the latter: The laboratory evidence on glycemia with both is similar.

There is no doubt that these substances in single doses by mouth lower the blood sugar promptly and substantially in normal men, dogs and rabbits. Hypoglycemic effects are observed within an hour or two (earlier when given with alkali) and they persist for hours. Indeed, it was the hypoglycemic manifestations seen on administration to nondiabetics for antibacterial purposes which led to their trial in diabetes.[2]

There is no doubt, also, that abnormal glycosuria and hyperglycemia are reduced or eliminated by these compounds in many patients with mild and moderately severe diabetes mellitus. Franke and Fuchs[1] showed eight examples of this, and they claim similar results in 80 per cent of fifty diabetics treated in Berlin for periods up to one year. After seven months of study in Hamburg, Bertram, Bendfeldt, and Otto reported successful control of diabetes in 25 of 28 older, mild diabetics not using insulin and replacement of insulin in 28 of 38 patients using it.[3] In younger patients with severe forms of the disease the sulfonamide had no effect. In some cases it appears uncertain from their data whether restriction of food or the sulfonamide was responsible for the reduction in sugar, but the evidence in favor of the drug is convincing in some of the trials. Unpublished results comparable to these are being obtained by laboratories and clinical investigators in this country.

Toxic side effects appear to be negligible and LD 50 dosages in animals are high. Skin reactions have been encountered not infrequently, but hematologic, hepatic and renal effects have seldom been observed. Crystalluria seems less likely to occur than with other sulfonamides, especially when alkali is given concurrently. Therapeutically effective blood sulfonamide levels of 10 to 15 mg. per 100 ml. are obtained with about 1 gm. daily, following larger priming doses for the first day or two. Blood levels fall slowly for days after administration is stopped.

There is general agreement among all investigators that the compound is totally ineffective in "pancreatectomy diabetes" and relatively so in alloxan diabetes. Ferner[9] and others[5c,8,10] have seen damage to the alpha cells of the islets after its use. These considerations, together with the fact that in most diabetics with favorable responses glycosuria does not recur promptly on stopping the drug, have led to the favored hypothesis that it acts by suppressing glucagon secretion. Other mechanisms of action have not been eliminated, however, among them accelerated release of insulin from the pancreas, inhibition of insulinase, other hepatic effects, and suppression of pituitary or adrenal function. It must be borne in mind that hypoglycemia in normals and apparent improvement of diabetes in diabetics can be produced at will by administration of insulin, hepatectomy, hepatic damage, and reduction in pituitary or adrenal activity. The fact that diabetes can be ameliorated and normoglycemia reduced by artificial means does not prove that the fundamental defect in diabetes has been improved in a physiological manner. Indeed, the fact that acidosis and severe diabetes cannot be controlled with the new compounds suggests that it is not.

No agent of this type is on the market yet in this country, but supplies have recently been distributed by two pharmaceutical firms for appraisal in diabetic patients in selected clinics and laboratories. Controlled experiments are being conducted, mechanisms of action explored and the effects of long continued administration watched closely. Results are being compared freely in joint conferences. Investigators feel as great an obligation to protect the diabetic public from possible exploitation and harm as to recognize and adopt a long sought therapeutically effective oral agent. The record of dependable and rational therapy in diabetes has been kept remarkably free from abuse and there is every

indication that the present developments will be no exception, in this country at least.

Those who witnessed the transient enthusiasm regarding the guanidine compound Synthalin (which also originated and was marketed in Germany until lenticular, hepatic and renal damage were encountered after sustained use) will welcome long, well-controlled studies by earnest and experienced investigators. To yield to the pressure of healthy diabetics for an easier way than insulin might do more harm than good. It is apparent that the type of diabetes which responds best to the new oral agents is also the type which is easiest to control by diet restriction. Since convenience is the only thing at stake, all concerned should be patient until convincing evidence concerning indications, mechanism of action, and particularly dangers from continued use is available, probably by the end of this year at the latest.

ARTHUR R. COLWELL, M.D.

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THIRTY-FIFTH ANNIVERSARY OF THE DISCOVERY OF INSULIN

This issue commemorates the thirty-fifth anniversary of the discovery of insulin. In it are recorded a personal recollection of Banting by Fulton, reminiscences of the work with Banting by Best, the clinical impact of the discovery as recalled by Joslin, and the printing in abridged form of the first report of the clinical use of the successful extract.

On the cover the first human subject to receive insulin, Leonard Thompson, is portrayed. He was fourteen years old when first treated, survived the vicissitudes of severe childhood diabetes and went on to live in good health until 1937 when he died of unrelated pneumonia. Had the precious antibiotics been available, they too might have brought even longer life to a human being who already owed most of his life to the work of two previously unknown but persistent and patient young investigators with an idea.

In considering the origin of their work it is apparent that the roots of their research stretch back almost timelessly into past medical and other scientific advances and experiments; the flower was the substance that consistently proved to be the hormone needed to make up the deficiency that characterizes experimental or human diabetes. Banting had surgical technic, a physiological and clinical appreciation of the possible role of a pancreatic extract which had to be obtained from the tiny endocrine islets imbedded in the mass of exocrine tissue. Best, a biochemically trained scientist, with unflagging energy, had the task of chemical separation and purification of the tissue extracts. Each needed the other and they were a model team for many others to copy.

Others before them, sensing the secret of the islets, had tried and failed to produce a consistently effective substance that was comparable to theirs. Readers of this Journal need no reminder that millions owe their lives directly or indirectly to the success of Banting and Best.

It is fitting therefore to commemorate on suitable anniversaries their achievement which, like so many medical discoveries, unites men of science by integrating knowledge and changing theory to fact or fancy. We grope towards the truth—limited by our own capacities—but discoveries like that of insulin give new minds the opportunity to retest old ideas or formulate

new ones.

The true nature of diabetes mellitus with its protean manifestations, complications, and variations of occurrence from childhood to old age, still eludes us. Indeed the exact structure, role, and locus of action of insulin are still sources of much provocative research and even controversy. In these days of complicated research with large grantors often pursuing the grantees to "do research," it may be timely to reflect on what was done with minimal assistance and meager equipment by two young men without titles or staff but with an idea and careful labor.

Reminiscences of the Discovery of Insulin

SIR FREDERICK BANTING

1891-1941

Banting was no ordinary investigator; indeed, he was not an ordinary man. I first met him in the autumn of 1923 in the house of Lady Osler at Oxford, and the occasion deserves to be recorded because it so happened that the Regius Professor of Medicine from Cambridge, Sir Clifford Allbutt, was visiting Lady Osler at the time. She introduced him to the young Canadian investigator and suggested that they go for a walk in the parks. Sir Clifford, who had always been greatly interested in young men who were making their way in scientific medicine, was fascinated by Banting, and he questioned him closely about the steps which had led to the discovery of insulin. He also questioned him about much else—art and literature, among other things—and he found that his young Canadian colleague was not only a physiologist, but in the Baconian sense he was also a "full man," for his interests extended to literature and art, and also to music (he was the best baritone in his class). At that time Banting was young, unsure of himself, and almost uncouth in dress and general appearance, but Sir Clifford, with his unerring tact, brought out the best that Banting had to offer, and when they returned to 13 Norham Gardens, Banting's eyes were glittering with a new light, and it was clear that Allbutt had inspired him.

In appraising Banting's various contributions it can be said that his work on insulin and other endocrine extracts gave meaning and significance to classical scientific method as we now recognize it. I should like also to reiterate the tribute which Dr. DuBois* has paid to his practical contributions, not only in the field of aviation medicine but also in military medicine generally. Banting had a genius for making practical applications, be it in a penetrating study of protective clothing, his introduction of the "clo" unit, or a study of aircraft equipment. He agitated for redesign of cockpits, strengthening the moorings of pilot seats and seat belts, and for moving the pilot's seat back far enough so that in the event of a head-on collision, or a nose-over landing, the pilot's face would not be thrown against the instrument panel.

I always admired Banting for quite another reason, namely, his common-sense attitude toward security regulations. Many of his colleagues in Canada and England were inclined to be overconscientious in matters of security, a trait which generally took the form of an unwillingness to discuss anything with anyone, with the result that there was little in the way of free exchange of ideas, even in a small military establishment, and there was no exchange whatsoever for well-screened and qualified individuals from outside who might have been able to lend the greatest assistance in the solution of a given military problem. Banting was never that way, but gauged his audience and spoke freely about classified material, and especially about instruments that fell into the classified categories, if he felt his colleagues or visitors had something worth while to offer. It was a kind of common sense that was rare, particularly during the early phases of the war. Everything was so hush-hush that one scarcely dared breathe. But not Frederick Banting. And as far

*Remarks of Professor Eugene F. DuBois following presentation of the Banting Medal at the Annual Meeting of the American Diabetes Association, June 1955. Diabetes 4:426-27, Sept.-Oct. 1955.

as I know, he was only occasionally in trouble with his secretive superiors!

Impressive, too, was Banting's unerring instinct in dealing effectively with the public; he felt the public was entitled to know what was going on in scientific laboratories—war or no war—and he took great trouble to explain the nature of scientific developments in language which the layman could readily comprehend. Few scientists were as conscientious as he in dealing with such things, and his efforts were warmly appreciated by the population at large.

In short, it seems to me that during the fifteen years since Banting's untimely death he has grown in stature on many scores, and his basic endocrine research looms large in the history of medicine, as well as his studies on design of decompression chambers, on decompression sickness, on acceleration, and on the ways and means of protecting flying personnel from the deleterious effects of high *g* forces. For these and many other things Banting's place in the history of our time is lastingly assured.

JOHN F. FULTON, M.D.
New Haven

Dr. Fulton, formerly Sterling Professor of Physiology at Yale University and now Sterling Professor of the History of Medicine, was invited by Professor Eugene F. DuBois to prepare this tribute to Sir Frederick Banting to be read with his, when Dr. DuBois was presented with the Banting Medal of the American Diabetes Association at the Annual Meeting, June 1955.

THE FIRST CLINICAL USE OF INSULIN

The clinical application of the discovery which Fred Banting and I hoped to make was in our minds from the very start of our partnership. This was inevitable because a part of Banting's motivation stemmed from an interest in a schoolmate in Alliston, Ontario, who died of diabetes. Recently my wife and I went to Alliston and helped to dedicate a portrait of Fred Banting which is to hang in the entrance hall of the Banting Memorial High School. We saw again the farm where he was born; where I first met his fine parents; and where our friend, Fred's older brother Thompson Banting, now lives. We drove along the road where Fred Banting walked to school and passed the house in which, we were told, the little diabetic girl had lived.

My own interest in diabetes began when my father's sister, who had gone from Nova Scotia to train as a nurse at the Massachusetts General Hospital, came to help my father in his small hospital on the Maine-New Brunswick border. She had developed diabetes some years previously and although her life was prolonged by the treatment administered by Dr. Joslin, she died a few years before insulin became available.

Every time one of our diabetic dogs responded to insulin we hoped that the effect on patients would be just as dramatic. When, in the autumn of 1921, we had demonstrated on 75 successive occasions in 10 completely depancreatized dogs, the invariably definite and frequently very impressive lowering of blood sugar after the administration of our pancreatic extracts, we considered that the phase of the discovery was complete. The clinical improvement in many of our animals was almost as convincing as the sweeping falls in blood sugar. We had concentrated on these main points: the lowering of blood sugar in completely depancreatized dogs and the improvement in their condition, but many other findings confirmed and supplemented these results.

It became necessary in the late autumn of 1921 in view of the intense experimental and clinical interest in our findings, to enlarge our team. Banting and I were forced to focus our interest on one series of problems and to make a very difficult selection. Banting decided that he would like to participate in the clinical application of our discovery. I chose the study of the effect of insulin on the respiratory quotient of completely depancreatized dogs for my M.A. thesis at that time because I thought that this was the central problem.

The records show that we had been making insulin by macerating whole beef pancreas, immediately after removal, in an equal volume of 95 per cent alcohol made acid by the addition of 0.2 per cent of concentrated hydrochloric acid. After thorough grinding of the mixture with mortar and pestle, the acid alcoholic extract was filtered and the clear filtrate evaporated to dryness, at first in a warm-air current, and later in an efficient laboratory vacuum-still which I had used during the previous year. In our second paper, which I have looked at again recently, it is noted that on Dec. 15, 1921, 200 mg. of the dried residue of ox pancreas extract were washed twice in toluol and then in 95 per cent alcohol and then dried again, and the resulting powder dissolved (or emulsified) in saline. At 10 a.m. this was given intravenously to a completely depancreatized dog. The blood sugar dropped from 0.37 per cent to .06 per cent in four hours. Our notes indicate that the improvement in the dog's condition was as dramatic as the fall in sugar.

In the extension of our research team, Professor Macleod assigned various problems to the members of his staff. The further purification of our insulin-containing extracts was entrusted to Prof. J. B. Collip in December 1921. Prof. Collip made rapid strides in the fractionation and concentration of the material, and contributed brilliantly in other ways to the development of the insulin researches.

Just after Christmas in 1921, Fred Banting came to me and suggested that I should make, as rapidly as possible, our best whole beef pancreas extract and that this should be the first insulin administered to a human case. This request came as a surprise but his sense of urgency was contagious and I immediately agreed. I suggested, however, that we should make an extract of fœtal pancreas which was much easier to process than whole beef glands and was much more potent. We now know that fœtal pancreas contains about seventeen times as much insulin per gram as the average whole beef pancreas does; we also know now that an extract of fœtal pancreas made by the exact procedure which we used in 1921 provides an excellent potent solution of insulin. Banting was in favor, however, of using the beef gland, and I can remember his exact words: "If we use fœtal calf pancreas they will say that the first extract used in patients was not made from a readily-available commercial source." Another argument in favour of normal beef pancreas was its availability. It might have taken us a week or more to collect sufficient fœtal glands to make a good-sized lot of insulin.

Banting and I frequently went together to the abattoir to collect fœtal pancreas or glands from adult animals. On this particular occasion I went alone and the abattoir authorities kindly immobilized a recently killed steer in a fairly convenient position so that I could remove the pancreas with aseptic precautions. This was taken back to the laboratory in a sterile container and worked up in the way I have described above. We had previously shown that it was possible to put the aqueous solution made from our acid alcoholic extract of normal beef pancreas through a Berkfeld filter. The final material in this particular case was a reasonably good looking product although of course it contained a very great deal of inert protein. Banting gave the first injection to himself and the second one to me. The next morning we had rather red arms but there was no other effect. We did not follow our own blood sugars. However, we did test the material on one of our diabetic dogs and obtained a fine fall similar to that which I have recorded above, and thus we established the potency of this extract. This was the solution which was sent over to the Toronto General Hospital and which was administered to several of the patients under the supervision of Dr. W. R. Campbell and Dr. A. A. Fletcher in Prof. Duncan Graham's department. The first person to receive an injection was Leonard Thompson whose history has been recorded in the clinical reports (*vide infra*). The first clinical publication from Toronto, which has often been overlooked, was in the Canadian Medical Association Journal, March 1922: "Pancreatic extracts in the treatment of diabetes mellitus," by F. G. Banting and C. H. Best, Department of Physiology; J. B. Collip, Dept. of Path. Chem.; W. R. Campbell and A. A. Fletcher, Dept. of Medicine, University of Toronto and Toronto General Hospital. A useful description of the early work which Banting and I had done is given in that report. It is recorded that the extracts given on January 11 (these are the ones which I have described above) were not as concentrated as those used at a later date and other than a lowered sugar excretion and a 25 per cent fall in blood sugar level no clinical benefit was evidenced. Banting described the results with Leonard Thompson and in some of the other early cases in somewhat more detail in his Nobel Prize Lecture and that paper should be consulted by those who are particularly interested.

The first injection of insulin was actually given to Leonard Thompson by the Senior Houseman on that particular ward—Dr. Ed. Jeffrey. Dr. Jeffrey was a close friend of Fred Banting's and of mine, and he told us all the details surrounding this first clinical trial. During the early stages of our work, Banting and I had not planned that our partially purified insulin which was so effective in dogs, would be the first material used on patients. We had often discussed these matters and hoped that the burden of the production of insulin for clinical use would be assumed by experienced chemical engineers. We were extremely happy, however, that a fall in blood sugar and a diminution of sugar excretion had been produced in the human subject by our extracts. The more concentrated and purified material made from the early type of extract by Dr. Collip soon became available and a great deal of further and very convincing clinical evidence was rapidly secured. After a relatively short period, however, Dr. Collip encountered serious difficulties in the preparation of active material and the supply of insulin for the Clinic completely stopped. Several of the patients, including a young girl, in whom my wife and I were particularly interested, died from lack of insulin after having been dramatically improved by the first injections which they received.

This failure of the supply of insulin created a major crisis. Fred Banting insisted that I should give up my study of physiological problems and take up the large-

scale preparation of insulin. Dr. Collip had returned to his professorial duties and no one else was available for this work. The struggle to recover the secret of making insulin in sufficient quantities for clinical use, was for me the most difficult and trying part of the whole insulin investigations. There was no time to approach the problem systematically and the only thing that seemed worth-while was to wage a night and day struggle in the hope that we might hit upon success. It may have been that a return to the use of a 0.2 per cent of concentrated hydrochloric acid in the extractive, or the introduction of the very efficient wind tunnel for rapid evaporation of our extracts, or the substitution of the lower boiling point acetone for alcohol as the original extractive, was the secret of the success which we achieved after a few weeks. More than one of these factors may have been important. In any case a consistent production of reasonable amounts of insulin was again made possible and the clinical work was started over again. The supply was at first not large and indeed over the summer months of 1922 the records show that not very much insulin was actually produced. The following table of the amounts sent to Fred Banting each month from what we called The Insulin Division of the Connaught Laboratories may be of interest. Further small amounts were probably sent directly to the Toronto General Hospital and to the Military Hospital at Christie Street. Some insulin was also made available for experimental work. The total was, however, very small and the product was of low potency—1 to 10 units per cc. as I remember it.

Insulin Supplied to Dr. Banting

June 1922	122½	cc.
July 1922	512	cc.
August 1922	390	cc.
September 1922	1,682	cc.

The recovery of the process for making insulin bridged the gap between the laboratory preparation and the large-scale commercial production. I have paid my tribute before to Dr. G. H. A. Clowes and the chemical engineers of Eli Lilly and Company and to my working partner in the Connaught Laboratories, Dr. D. A. Scott, who helped with further modifications and improvements in the large-scale preparation of insulin. There are many other names which should be mentioned and I can select only a few. The contributions of E. A. Doisy, M. Somogyi, and P. A. Shaffer, of the late Harold Ward Dudley, of P. J. Moloney and D. M. Findlay, will not be forgotten. Many different processes were soon developed for the further purification and concentration of the active material which we had found. This is not the place to review the many important steps by which insulin has been made a more efficient therapeutic agent. When the active substance has been synthesized it is possible that modification can be introduced which will further improve the antidiabetic effects of the hormone.

CHARLES H. BEST, M.D.
Toronto

A PERSONAL IMPRESSION

It is fitting to honor Leonard Thompson, the first patient to receive insulin, by placing his picture upon the cover of DIABETES. He had the courage to volunteer for an experiment. He was not like the dog, a passive participant, but an active member of the diabetic team. He stands out as an example of thousands of diabetics who have followed their doctors' advice, often bizarre, and have lived an honest diabetic day, not for themselves alone, but for the benefit of mankind. Would that they, especially those in the starving decade before insulin, could be immortalized as Rodin did those six emaciated burghers of Calais, who with halters around their necks, expecting death after its year-long siege, surrendered to Edward III to save their city.

For a quarter of a century I had been treating, or rather fighting, diabetes, when I heard a rumor of a surprising discovery by two young men in Toronto and went to New Haven in December 1921 to hear Banting speak about his experiment before the American Physiological Society. As we listened we physicians became so excited over what we learned and asked so many questions that the customary serenity of the meeting of that elite organization was upset and some of the members showed they regretted our presence. Banting spoke haltingly, Macleod beautifully. The possibility of mistakes in the work was fully exploited by those who discussed the paper in a skeptical but on the whole in a sympathetic way. A few months later Banting and Best and their clinical colleagues, Campbell and Fletcher, in Toronto showed us their early cases, but the full impact of the discovery did not fully dawn upon me until I learned I was to receive insulin for trial with my own patients. I remember well staying awake all night the day before it was to arrive. The first unit I gave to Miss Mudge, my severest patient, a nurse, on Aug. 7, 1922. She had obeyed the rigid regime. During her five years of diabetes her weight had fallen from 157 to 72 pounds, but she remained sugar free. She was nearly bedridden and, I recall, had gone over a flight of stairs in her home (oddly enough on the site of the New Hospital Teaching Clinic), but once in nine months. I watched her come back to life and go on in later years

to care for her mother instead of her mother's taking care of her. After four weeks of insulin, she walked four miles, and in seven months she gained twenty pounds. She lived another twenty-five years happily until she died suddenly of coronary thrombosis.

By Christmas of 1922 I had witnessed so many other near resurrections that I realized I was seeing enacted before my very eyes Ezekiel's vision of the valley of dry bones—Ezekiel XXXVII, 2-10:

> ". . . and behold, there were very many in the open valley; and, lo, they were very dry.
>
> And he said unto me, Son of Man, can these bones live?
>
> And . . . lo, the sinews and the flesh came up upon them, and the skin covered them above: but there was no breath in them.
>
> . . . Thus saith the Lord God: Come from the four winds, O breath, and breathe upon these slain, that they may live.
>
> . . . and the breath came into them, and they lived, and stood up upon their feet, an exceeding great army."

Colonel Palmer, my standard Case Number 632, a most brilliant young officer in the Canadian Army whose career was shattered by diabetes just before the first World War, came back for insulin. When he saw the children, his first reaction was: "Now they make a noise." Formerly they sat with protruding bellies, silent for hours, resignedly consuming their washed 3 per cent vegetables. Yet today of those feeble creatures there is many a one alive, breathing and standing upon his own feet. Von Noorden shuddered and turned aside at the sight of one of them a quarter of a century ago, but now he has passed on, and little Ruth is now working in a doctor's office in Chicago. For Christmas in 1922 the group of my first insulin users, numbering 83, sent a "round-robin" letter of thanks to Mr. Lilly in Indianapolis. He replied with the present of a doll to the girls, which they promptly named "Lilly," and to the boys, an insulin syringe set.

There was almost a tinge of regret in several of us over the discovery of insulin, because it had come so soon. It was known that much was being learned about the disease and we feared intensive effort would stop. Children were living two years instead of one; adults six years instead of five; an occasional patient outlived a normal life expectancy and we were discovering day by day mistakes that we had made in dietetic treatment and learning how they could be corrected and the metabolism of the diabetic preserved and strengthened. We argued by analogy, if a similar improvement occurred in a group of cancer patients, how it would be acclaimed! We knew that progress was being made and that the whole field of the betterment of diabetes by existing methods had yet to be explored. Although it still was a Cyrano de Bergerac fight, the joy of working and fighting was uppermost, even though it was realized the cause might be lost. Never before had such a high pitch of endeavor been evident in all centers in diabetes.

Then came insulin and what a reaction followed. "Now, Dr. Joslin, you will have no more diabetics to treat," was the common saying. The relaxation was as great as that I saw Nov. 11, 1918, in France the day of the armistice. In the twinkling of an eye, the whole atmosphere changed. Instantly salutes, which before 11 o'clock were alert and snappy, by noon had become informal and sloppy. Only one thought possessed the thoughts of the American soldiers—namely, to get home.

The finding of insulin by Banting and Best was unusual in that it was an anticipatory discovery. Then there were comparatively few diabetics in the world, because the average age at death of people generally was around forty years, whereas the onset of two-thirds of all cases of diabetes occurs above the age of forty years. Future generations therefore will rise up and call them blessed even more than those in their own generation.

It is a great satisfaction today to sense that same old enthusiasm, zeal and endeavor to prevent and treat diabetes which existed just before insulin was discovered. But the attack upon the disease is now on a broader basis. Then we were fighting a battle, but now we are conducting a campaign. Then the object of the encounter was to defeat diabetic coma, which took the lives of two-thirds of all the patients; today our campaign is to prevent and overcome complications in the eyes, circulation and kidneys. The battle ended in a quick death in unconsciousness, the campaign involves a lingering illness often with pain and despair, yet now there is more hope because we are convinced and have found the proof that such a sad outcome can be avoided by meticulous control of the disease, particularly in its early years, temporarily utilizing undernutrition diets, supplemented by insulin.

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PANCREATIC EXTRACTS IN THE TREATMENT OF DIABETES MELLITUS

PRELIMINARY REPORT BY F. G. BANTING AND C. H. BEST, *Dept. of Physiology*
J. B. COLLIP, *Dept. of Path. Chemistry*
W. R. CAMPBELL AND A. A. FLETCHER, *Dept. of Medicine, University of Toronto, and Toronto General Hospital*

Since the year 1889, when von Mering and Minkowski produced severe and fatal diabetes by total removal of the pancreas in dogs, many investigators have endeavoured to obtain some beneficial effect in diabetes mellitus, either by feeding pancreas, or by administration of pancreatic extracts.

. . . The whole question has been reviewed recently by Allen: by him, and, indeed, by the majority of recent writers, it is usually stated that pancreatic extracts have no clinical value whatsoever. During the past ten months, two of us (F.G.B. and C.H.B.), working in the Department of Physiology of the University of Toronto, have reinvestigated the problem. Certain of the results obtained have already been published, others are now in press. These may be briefly reviewed here.

Believing that extracts of the pancreas, as usually prepared, did not satisfactorily demonstrate the presence of an internal secretion acting on carbohydrate metabolism, because the active principle was destroyed by the digestive enzymes also present in such extracts, attempts were made to eliminate these enzymes. In the first experiments, this was done by taking advantage of the fact that the acinous tissue (from which the digestive enzymes are derived) but not the insular tissue of the pancreas degenerates in seven to ten weeks after ligation of the pancreatic ducts. Extracts were therefore made with ice-cold Ringer's solution, of degenerated pancreatic tissue removed ten weeks after the ligation of the ducts. The extract obtained by this procedure, when injected intravenously or subcutaneously into diabetic dogs, invariably caused a marked reduction in blood sugar and in the amount of sugar excreted in the urine. It also enabled a diabetic dog to retain a much higher percentage of injected sugar than it otherwise would. Extracts of liver or spleen, prepared in the same manner as the extracts of degenerated pancreas, were found to have neither of these effects. The active principle of the extract of degenerated pancreas was destroyed by boiling in neutral or acid solution or by incubating for two hours at body temperature with pancreatic juice.

In later experiments, it was found that the pancreas of foetal calves of under five months development did not contain proteolytic enzymes, thus confirming the observations of Ibrahim. By extracting such foetal pancreatic tissue, a highly potent and readily procurable preparation was obtained. . . . A method was finally evolved by which an active extract, which would retain its potency for at least one month, could be obtained from normal adult ox pancreas. Daily injections of pancreatic extract (foetal calf or adult beef pancreas) prolonged life of a completely diabetic dog to seventy days, at the end of which time the animal was chloroformed. Allen states that in his experience completely diabetic dogs do not live more than fourteen days. The first results of a study of the respiratory exchange in completely diabetic dogs, before and after administration of extract, showed that the extract confers on the diabetic animal the power to burn carbohydrates. Thus, in a diabetic dog, on starvation or lean meat diet, the respiratory quotient was found to be in the neighborhood of 0.7. The ingestion of carbohydrate caused no

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rise in the CO_2/O_2 ratio, but when preceded by an injection of extract gave a value which approached I.O., indicating that carbohydrate was being burned. Besides the above, it should be recorded that the administration of extract very quickly caused striking improvement in the various symptoms known to be characteristic of complete pancreatectomy.

As the results obtained by Banting and Best led us to expect that potent extracts, suitable for administration to the human diabetic subject, could be prepared, one of us (J.B.C.) took up the problem of the isolation of the active principle of the gland. As a result of this latter investigation, an extract has been prepared from the whole gland, which is sterile and highly potent, and which can be administered subcutaneously to the human subject. The preparation of such an extract made possible at once the study of its effects upon the human diabetic, the preliminary results of which study are herein reported.

. . . Up to the present time, February 22nd, 1922, the effects of these preparations have been observed in seven cases of diabetes mellitus and it is now evident that certain definite results can be obtained by their administration. The effects observed in depancreatized animals have been paralleled in man. The fall in blood sugar occurs and in two cases, repeatedly examined, a rise in the respiratory quotient, indicating carbohydrate utilization, occurs more or less coincidently with the attainment of a normal blood sugar level. Patients report a complete relief from the subjective symptoms of the disease. The sugar excretion shows marked decrease or, if dosage be adequate, disappears. Ketonuria is abolished, thus confirming a similar observation by Collip in diabetic animals, (results as yet unpublished). These results taken together have been such as to leave no doubt that in these extracts we have a therapeutic measure of unquestionable value in the treatment of certain phases of the disease in man. In agreement with observations of other investigators on laboratory animals, it has been found that without careful control severe toxic reactions may be encountered and this will undoubtedly be a factor in the evaluation of the ultimate therapeutic utility of the method.

The following case report illustrates these observations:

Name.—L. T. (Boy), *Aged*—14.

Admitted to the Medical Wards, Toronto General Hospital, December 2nd, 1921.

Present Illness.—About December 1919, he was taken to his family physician because he had been wetting the bed at nights, and also because his ankles became swollen occasionally. One month later, sugar was found in the urine. He states that at this time he was in good health, his appetite was somewhat excessive, but no increased thirst was complained of. Careful dietetic regulation was prescribed and he states that he adhered to this diet fairly well. This his family physician will not confirm. Fasting was also tried apparently without success. The glycosuria persisted, he began to lose weight, frequency of micturition, both day and night, increased up to the time when his physician recommended admission to hospital.

Past Illness.—Always healthy up until two and one half years ago, with the exception of an attack of chicken-pox at the age of ten and, of discharging ear for two years as a baby.

Personal History.—Born in Canada, went regularly to school, able to work well up to time of onset of present illness. Has always been fond of sweet food and previous to the onset of this condition ate freely of candy.

Family History.—Mother and father, one brother and two sisters, all in good health. No diabetes or other familial diseases known.

Examination.—On admission he was poorly nourished, pale, weight 65 pounds, hair falling out, odour of acetone on the breath, tonsils and teeth in good condition, abdomen large and tympanitic. Blood pressure 100-70. He appeared dull, talked rather slowly, quite willing to lie about all day. Hands show marked xanthochromia. No findings of note in examination of cardio-vascular, respiratory, abdominal systems or of the blood. The urine at the time of admission was strongly acid, specific gravity 10.30 to 10.40. The test for sugar strongly positive. Rothera and ferric chloride tests for ketones strongly positive. 24 hours amount of urine, 3-5 litres. Blood sugar 5.8 mg. per c.c.

Treatment.—He was put to bed and was quite content to remain there most of the time. However, when he wished to do so, he was allowed to get up and wander about the ward, which he did very little during the first month. His diet was as follows:—

Dec. 2nd.—5, 10 and 15% vegetables as much as desired.

Dec. 11th.—60 grams lean meat daily added to diet.

Dec. 15th.—4 bran cakes daily added to diet.

Jan. 4th.—Daily ration to consist of 50 grams lean meat, 5 and 10% vegetables, and fruits and bran cakes to make up exactly 100 grams of carbohydrates per day. Clear broth, cocoa, tea and coffee in moderation. Total intake about 450 calories.

No further change in diet was made.

This case was one of severe juvenile diabetes with ketosis. Previous to admission, he had been starved without evident benefit. During the first month of his stay in hospital, careful dietetic regulation failed to influence the course of the disease and by January 11th his clinical condition made it evident that he was becoming definitely worse.

The extracts given on January 11th were not as concentrated as those used at a later date, and, other than a slightly lowered sugar excretion and a 25% fall in the blood sugar level, no clinical benefit was evidenced.

Daily injections of the extract were made from January 23rd to February 4th (excepting January 25th and 26th). This resulted in immediate improvement. The excretion of sugar became much less. On days of treatment, this varied from 7.5 gms. to 45.1 gms. compared with a previous amount well over 100 gms. daily. The acetone bodies disappeared from the urine. The boy became brighter, more active, looked better and said he felt stronger. No extract was given from February 5th to February 15th. During this time sugar again appeared in the urine in large amounts along with traces of acetone. Administration of extract in smaller doses after February 16th again resulted in lowered sugar excretion and disappearance of acetone from the urine. . . .

. . . Although the other six patients treated by these extracts were all favourably influenced by its administration, particular reference might be made to one—a severe case who had been excreting 20 gms. of glucose on a diet containing 10 gms. carbohydrate and 24 hundred calories per day. Following injection of the extract his urine became sugar free, and he obtained complete relief from severe depression and extreme lassitude. Respiratory quotients in this same case showed a definite rise after injection of the extract, confirming the increased utilization of carbohydrate. All patients were improved clinically. . . .

SUMMARY

Following the production of what appears to be a concentrated internal secretion of the pancreas and the demonstration of its physiological activity in animals, and, under careful control, its relatively low toxicity, we are presenting a preliminary report on the pharmacological activity of this extract in human diabetes mellitus. Clinical observations at this juncture would appear to justify the following conclusions:—

(1) Blood sugar can be markedly reduced even to the normal values.

(2) Glycosuria can be abolished.

(3) The acetone bodies can be made to disappear from the urine.

(4) The respiratory quotient shows evidence of increased utilization of carbohydrates.

(5) A definite improvement is observed in the general condition of these patients and in addition the patients themselves report a subjective sense of well being and increased vigor for a period following the administration of these preparations.

For their hearty co-operation and kindly assistance and advice, we have great pleasure in presenting our best thanks to Professor J. J. R. Macleod of the Department of Physiology, to Professor V. E. Henderson of the Department of Pharmacology, to Professor J. G. Fitzgerald of the Department of Hygiene, and to Professor Duncan Graham of the Department of Medicine of the University of Toronto.

Book Reviews

CURRENT CONCEPTS OF DIABETES MELLITUS WITH SPECIAL REFERENCE TO OCULAR CHANGES: *By L. Benjamin Sheppard, M.D., Assistant Professor of Ophthalmology, Medical College of Virginia, Richmond, Virginia. Publication No. 210, American Lecture Series. A monograph in American Lectures in Ophthalmology, edited by Donald J. Lyle. $3.75, pp. 90, Charles C Thomas, Springfield, Ill., December 1954.*

Dr. Sheppard has written a scholarly and readable monograph reviewing and collating the literature of the years 1940 to 1950. Studies during this decade have drawn a reasonably clear distinction between diabetic and atherosclerotic retinopathy and the author concludes that the pathological changes in the retina are apparently closely related to the disturbances in diabetic metabolism.

The volume contains suggestions to aid the ophthalmologist in the evaluation of the fundus. Current and potential trends in research are outlined.

THE CLINICAL CARE OF THE DIABETIC. *By James J. Short, M.D., F.A.C.P., Associate Professor of Medicine, School of Medicine, College of Medical Evangelists; Senior Attending Physician, Los Angeles County General Hospital, Los Angeles, California. $3.95, pp. 84. San Lucas Press, Los Angeles, California, 1955.*

This recently published book is an addition to the gradually increasing library of small-sized books devoted to the subject of diabetes mellitus and the management of the diabetic patient. It is written for the clinician rather than for the patient, and contains within its 84 pages a discussion of the etiology and pathology of the disease, its dietary management and insulin regulation, and the treatment of complications. Of necessity, the discussions are brief and many of the precise details of management of specific problems have not been included. Nevertheless, the physician who has little time for reading and who desires a book which will refresh his memory quickly may find that this book serves his purpose.

Prevention of Chronic Disease in Old Age

The time is ripe to extend the concept of prevention to our aging population. In many instances, prevention of chronic diseases and disabling accidents is possible. In almost all cases, prevention of prolonged and total disability is possible. Never before has medical science had such a wealth of pertinent knowledge and effective technics ready for application to the health problems of older people.

If we are to apply these advances effectively to the health problems of our aging population, however, we must begin to build for better health far in advance of that 65th year which supposedly signifies the onset of old age. The aim in our personal health practices, as well as in our professional relationships and in our community programs, should be to prevent the serious, disabling conditions associated with old age.

There are several ways of looking at the possibilities of this emphasis on prevention. It would give the older people a larger measure of health and happiness and would free them and their families of a considerable economic burden. It would give the community a deeper satisfaction in its efforts to meet one of its most urgent problems, as well as substantial reductions in the costs of long-term care of the sick. And it would mean that a large proportion of old people requiring sheltered care would enter the institutions in better health than many of those now receiving institutional care.

To achieve these results, we will have to emphasize prevention all along the line: chronologically, in the lives of individuals; and organizationally, in our education of professional personnel, in all our hospitals and related facilities, and in our community programs and services.

Better health for the aged may often begin before birth. Dr. Joseph P. Höet of Louvain University recently reported that by discovering a prediabetic condition among mothers during pregnancy and by treating those with an abnormal blood sugar and their offspring, there is an excellent chance of preventing a high proportion of cases of diabetes in adults.* The disease may be present in a latent stage from birth.

From "Prevention of Chronic Disease in Old Age" by Leonard A. Scheele, M.D., Surgeon General, U. S. Public Health Service in *Public Health Reports*, May 1954.

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*Diabetes 3:1-12, January-February 1954.

ABSTRACTS

Abbou, R.; Lestradet, H.; and Azerad, E.: THE CLINICAL VALUE OF THE INTRAVENOUS INDUCED HYPERGLYCEMIA TEST. Presse méd. *63*:333-35, March 5, 1955.

A 50 per cent glucose solution is administered intravenously at a rate of 0.33 gm. per kg. of body weight. The total injection is completed in two minutes (40 cc. of 50 per cent glucose given in two minutes in a 60-kg. subject). Blood sugar determinations are performed every fifteen minutes for a period of sixty minutes after the glucose administration. Blood is withdrawn from the ear lobe and the micro-method of Somogyi-Nelson was used. The subjects were fasting. Normal subjects showed a return of blood sugar levels to the normal glycemic levels within sixty minutes, unlike diabetic patients who maintained hyperglycemic levels during this time. (French)

Allegretti, Niksa; Vukadinovic, Gjorgje; and Rabadjija, Luka: INSULIN SENSITIVITY IN ADRENALECTOMIZED RATS TREATED WITH ASCORBIC ACID AND DESOXYCORTICOSTERONEACETATE (DCA). Am. J. Physiol. *180*:508-10, March 1955.

Experiments are reported in the adrenalectomized rat dealing with sensitization to insulin action by ascorbic acid and by DCA. It had previously been noted that both agents produce sensitization to insulin in the intact animal. After adrenalectomy, only DCA brought about sensitization. This difference in behavior is ascribed to differences in sodium retention before and after adrenalectomy. In either type of preparation DCA effects sodium retention; but its effect is greater and insulin sensitization more pronounced in rats fed with the usual laboratory supply of food than in those deprived of sodium chloride.

Arkin, W.; and Hryniewska, H.: INSULIN SHOCK THERAPY OF RETROBULBAR NEURITIS. Ophthalmologica *128*:107-14, August 1954. (Abstracted from Am. J. Ophth. *39*:920, June 1955.)

In a series of thirty cases of retrobulbar neuritis, mild insulin shock therapy (30 to 40 units intravenously daily for four to six days) was remarkably effective in reducing or abolishing the central scotoma and in improving visual acuity. The authors consider most of their cases as early forms of multiple sclerosis.

Ashare, Raymond; Moore, Richard; and Ellison, Edwin H.: UTILIZATION OF GLUCOSE, FRUCTOSE, AND INVERT SUGAR. A.M.A. Arch. Surg. *70*:428-35, March 1955.

Comparative infusions of 10 per cent glucose, fructose, and invert sugar, at an average rate of 1 gm. per kg. body weight per hour, were given to three groups of resting patients. Each patient served as his own control for two and, occasionally, three of the sugars used. Blood sugar, lactic acid, and inorganic phosphorus levels and urinary losses of sugar, sodium, and potassium were measured for a period of six and a half hours from the time of infusion. Infusions of fructose and invert sugar led to smaller losses of urinary sugar than of glucose in normal subjects and in patients with pancreatic disease and hepatitis. However, the difference did not exceed 9 gm. per infusion in any of the three groups studied. In general, the diuretic effect was slightly less marked with fructose and invert sugar. In normal subjects, the loss of sodium was slightly more pronounced with fructose and invert sugar than with glucose. Potassium losses were a little greater after fructose but not after invert sugar infusions. Serum lactic acid levels were consistently higher with fructose and invert sugar than with glucose in nearly all patients, including those cases in which the urinary loss of sugar with fructose and invert sugar was greater than with glucose. Serum inorganic phosphorus fell in nearly all patients, without a definite pattern in relation to type of sugar infused or patient group. Symptomatic post-infusional hypoglycemia was observed with glucose but not with fructose or invert sugar in three patients with hepatitis. In patients undergoing major surgical procedures under general anesthesia, a fall in hepatic glycogen was always observed with infusions of saline. This fall in hepatic glycogen could be prevented in many patients by infusion of any of the three hexoses studied. Fructose (followed by invert sugar and glucose in this order of decreasing effectiveness) has the greatest ability to form hepatic glycogen in dogs under pentobarbital (Nembutal) anesthesia. This observation suggests that fructose may be the most useful sugar in patients with depleted hepatic glycogen reserves.

Bond, Bar Dee; and Spitzer, John J.: EFFECTS OF HEPARIN ON CARBOHYDRATE METABOLISM IN THE RABBIT. Am. J. Physiol. *180*:575-79, March 1955.

The effects of heparin on carbohydrate metabolism in the rabbit were investigated. The following results were obtained. (a) Heparin causes a highly significant rise in the normal fasting blood glucose level, which can be prevented by the previous administration of Priscoline. (b) Heparin does not significantly affect the hyperglycemia induced by small amounts of epinephrine,

although a slight increase in the duration and intensity can be observed. (c) Heparin has no significant effect on the hyperglycemia induced by glucagon, the hyperglycemic factor of the pancreas. (d) Heparin significantly diminishes the intensity of the insulin-induced hypoglycemia. (e) On the basis of the results, it is postulated that multiple injections of heparin cause an endogenous release of epinephrine in the rabbit.

Booker, Walter M.; Tureman, James R.; DaCosta, Frances M.; Poulson, John; and Mitchell, Samuel Q.: RELATIONSHIP BETWEEN GLUTATHIONE AND ASCORBIC ACID IN ADRENOCORTICAL FUNCTION. Am. J. Physiol. *181*:371-74, May 1955.

In studies on mice, the authors observed that cortisone prevents a diminution in the adrenal ascorbic acid during stress but has no effect on the adrenal cholesterol. No significant difference was noted between the whole-body vitamin C of stressed and unstressed intact and adrenalectomized mice. Like ascorbic acid, glutathione increases survival against the stress of cold in intact and adrenalectomized mice, although less extensively in the latter.

Breitzke, G.: DIABETES TREATMENT IN A RURAL DISTRICT—1946 TO 1953. Deutsche med. Wchnschr. *80*: 221-23, Feb. 11, 1955.

Treatment of diabetes in a rural district of Germany, based on the use of a diet rich in carbohydrate and low in fat during the years 1946 to 1953, is reported. Patients who prior to 1946 were accustomed to a diet rich in fat required less insulin on this regimen. The advantage of a diet low in fat is particularly emphasized. Additional evidence is the low incidence of new cases of diabetes in the first postwar years, when a diet poor in fats was the rule. (German)

Brown, H.; Sanger, F.; and Kitai, Ruth: THE STRUCTURE OF PIG AND SHEEP INSULINS. Biochem. J. *60*:556-65, August 1955.

The structures of pig and sheep insulins have been determined by subjecting them to partial hydrolysis and comparing the peptide chains so produced with those obtained from cattle insulin following similar treatment. While the amino acid sequences in the phenylalanine chains of all three insulins are identical, there are species differences in the glycyl chains in positions 8 to 10 inclusive. In cattle insulin, this sequence is -alanine-serine-valine-; in pig insulin, -threonine-serine-isoleucine-; and in sheep insulin, -alanine-glycine-valine.

Bulgarelli, R.; and De Matteis, F.: GLYCOGENOSIS AND HEPATIC SCLEROSIS REVEALED BY NEEDLE PUNCTURE BIOPSY OF LIVER: ATYPICAL GIERKE'S DISEASE OR SECONDARY GLYCOGENOSIS? Minerva pediat. *6*:981-88, Dec. 31, 1954. (Abstracted from J.A.M.A. *158*:147, May 14, 1955.)

The authors report an atypical case of glycogenosis (Gierke's disease) associated with hepatic sclerosis, the onset of which had been favored by the intake of watered wine from a very early age.

Clausen, Roy E., Jr.; and Hogan, Henry W.: A REVIEW: RECENT CONCEPTS IN NEURITIS. Am. J. M. Sc. *229*:103-115, January 1955.

The authors review the clinical manifestations of neuritis; survey the nutritional, infectious-allergic, vascular-hematogenous, toxic-metabolic, and familial states associated with it; cite the present lack of pathophysiologic knowledge in this disease; and comment on the current chaotic status of therapy caused by conflicting claims for such agents as B complex vitamins, B_{12}, BAL, pregnant mammalian liver extract, ACTH, and cortisone in diabetic and other types of neuritis.

Clowes, G. H. A.; and Keltch, A. K.: GLUCOSE, MANNOSE, AND FRUCTOSE METABOLISM BY ASCITES TUMOR CELLS: EFFECTS OF DINITROCRESOL. Proc. Soc. Exper. Biol. & Med. *86*:629-34, August-September 1954.

Ascites tumor cells derived from Ehrlich carcinoma or sarcoma 180 consume glucose, mannose, or fructose, but not galactose, xylose, or arabinose. Under anaerobic conditions, the hexose consumed is approximately accounted for by lactate produced. The consumption of glucose and the production of lactate therefrom under anaerobic conditions are markedly stimulated by dinitrocresol (DNC). In contrast, the anaerobic consumption of fructose and of lactate production therefrom and the anaerobic production of lactate from mannose are not stimulated by DNC. The aerobic consumption of lactate is raised by DNC to nearly the anaerobic levels; there is thus strong poisoning of the Pasteur effect. The aerobic consumptions of mannose and fructose are less influenced by DNC, but the production of lactate is raised at higher concentrations of DNC to the anaerobic level.

Cohn, Clarence; Shrago, Earl; and Joseph, Dorothy: EFFECT OF FOOD ADMINISTRATION ON WEIGHT GAINS AND BODY COMPOSITION OF NORMAL AND ADRENALECTOMIZED RATS. Am. J. Physiol. *180*:503-07, March 1955.

The weight gains and body composition of young adult adrenalectomized and normal rats were measured under the condition of ad libitum and of force feeding. The force-fed adrenalectomized rats gained weight and had a body composition similar to that of tube-fed controls. By contrast, adrenalectomized rats allowed to eat ad libitum lose body fat and gain less weight (because of an inadequate food intake) than control animals eat-

ing in a like fashion. The findings indicate that the over-all rate of utilization of the foodstuffs by the animal lacking his adrenals does not differ from normal when the food intake is 'optimal.' Force-fed normals contain more body fat than normal animals eating ad libitum which receive the same diet and gain the same amount of weight.

Demis, Dermot J.; and Rothstein, Aser: RELATIONSHIP OF THE CELL SURFACE TO METABOLISM. XII. EFFECT OF MERCURY AND COPPER ON GLUCOSE UPTAKE AND RESPIRATION OF RAT DIAPHRAGM. Am. J. Physiol. *180*:566-74, March 1955.

Both aerobic and anaerobic glucose uptakes by excised rat diaphragm are rapidly inhibited by low concentrations of mercuric chloride. Mercuric chloride inhibits endogenous respiration and anaerobic lactic acid production slowly. The inhibition gradually increases with time after an initial lag period. Approximately 10 times as much mercury is required to inhibit respiration as to inhibit glucose uptake. The mercury inhibition of glucose uptake by intact diaphragm can be rapidly reversed by several sulfhydryl compounds. However, the inhibition of respiration is not appreciably reversed once it has developed. In homogenates of rat diaphragm, mercury rapidly inhibits respiration; this inhibition can be rapidly reversed by cysteine. Cupric chloride acts on intact diaphragm in a manner similar to that of mercury, blocking glucose uptake immediately but inhibiting respiration only after a long lag period. Respiration is more sensitive to copper than is glucose uptake. By histochemical methods, it can be shown that mercury taken up by the cells is localized in the periphery of the cell during the first twenty minutes. Thereafter, it penetrates into the interior of the cell in increasing amounts. Most of the mercury added to the medium is bound by the cells. The rate of binding follows first-order kinetics for the first twenty minutes. Thereafter, with high concentrations of mercury, there is a continued uptake of mercury at a lower rate. The various effects of mercury and copper are compatible with the hypothesis that certain reactions necessary for glucose uptake are located in the periphery of the cell or on the cell surface, whereas the respiratory enzymes are located within the interior of the cell.

D'Ermo, F.; and De Ferrari, G.: ELECTROPHORETIC STUDY OF THE PLASMA PROTEINS IN PATIENTS SUFFERING FROM SO-CALLED ALBUMINURIC RETINOPATHY. Boll. d'ocul. *33*:653-57, September 1954. (Abstracted from Am. J. Ophth. *39*:437-38, March 1955.)

Blood plasma of patients suffering from chronic glomerulonephritis with retinopathy was studied by use of paper electrophoresis. A decrease in albumin and a relative increase in the globulin fractions were found. Similar changes occur in patients suffering from diabetes and from hypertension without retinal disease.

Dury, Abraham: RESPONSES OF LIVER LIPID FRACTIONS, LIVER AND PLASMA ELECTROLYTES SHORTLY AFTER ALLOXAN ADMINISTRATION IN RAT. Proc. Soc. Exper. Biol. & Med. *86*:646-49, August-September 1954.

The responses of the lipid fractions of liver and liver and plasma electrolytes to alloxan administration were determined at 4, 24, and 72 hours. The adrenal ascorbic and cholesterol concentrations were also measured as indices of adrenocortical activation in these animals. Besides the known responses of hyperglycemia and decreased liver glycogen content, there were similar changes in other chemical constituents in all groups—an increased neutral fat and decreased liver potassium content and an increased plasma potassium level. The changes in the tissue chemistries of the 4 and 24-hour groups after alloxan could be interpreted as signs of an hepatoxic action of alloxan, or responses of a stress type which were adrenocortically conditioned. The nature of the altered chemistries 72 hours after alloxan was essentially the same in intact and adrenal-demedullated rats.

Editorial: NEW INSULINS. Orientación Médica *4*:16, Jan. 7, 1955.

A discussion is presented of the rate and duration of action of different preparations of insulin including soluble insulin, protamine zinc insulin, globin zinc insulin, NPH insulin, di-insulin (a mixture of soluble insulin and isoinsulin with effect similar to that of protamine zinc insulin), insulosan (insulin diluted in subtosan, with effect also comparable to that of protamine zinc insulin) and insulin-zinc suspensions. (Spanish)

Editorials and Comments: RESTRICTIVE DIETS. J.A.M.A. *158*:123, May 14, 1955.

Dietary restrictions for an acute emergency lasting only a few days, such as diabetic acidosis or a gastrointestinal upset, are easily tolerated; but if dietary restriction becomes a part of the treatment of a chronic disease, numerous difficulties must be met. The physician must prescribe a diet that is palatable, satisfying in quantity and quality, productive of adequate bodily energy, and balanced. In addition, it is desirable that the diet be simple and flexible in regard to items that can be substituted from day to day.

When one is treating a person with diabetes, the objective is to provide sufficient calories to keep the patient well and strong enough to allow a gain in weight. Diabetes can be controlled adequately with a liberal diet with adjusted doses of insulin.

Elgee, Neil J.; and Williams, Robert H.: EFFECTS OF THYROID FUNCTION ON INSULIN-I^{131} DEGRADATION. Am. J. Physiol. *180*:13-15, January 1955.

The degradation of insulin labeled with radioactive iodine (I^{131}) in the rat was increased by the administration of thyroxine or triiodothyronine and decreased by thyroidectomy.

Elgee, Neil J.; and Williams, Robert H.: PITUITARY AND ADRENAL INFLUENCES ON INSULIN-I^{131} DEGRADATION. Am. J. Physiol. *180*:13-15, January 1955.

The degradation of insulin labeled with radioactive iodine was profoundly diminished in rats after hypophysectomy. It was postulated that this phenomenon might contribute to the insulin hypersensitivity of the hypophysectomized animal. Adrenalectomized rats and rats treated with hydrocortisone and/or growth hormone showed little alteration in insulin-I^{131} degradation, and no evidence was obtained to indicate that alterations of carbohydrate metabolism produced by such conditions are related to altered insulin degradation.

Emerson, J. D.: DEVELOPMENT OF RESISTANCE TO GROWTH-PROMOTING ACTION OF ANTERIOR PITUITARY GROWTH HORMONE. Am. J. Physiol. *181*:390-94, May 1955.

The author presents data showing that treatment of the Norway rat with a constant daily dose of pituitary growth hormone of bovine origin leads to a period of rapid growth, then one of reduced growth, followed in turn by a complete or near-complete absence of growth; the dose of hormone administered remains unchanged. Increasing the dosage leads to renewed growth, which is followed by a plateauing of the growth curve at a higher level. It has been shown that this result can be obtained with both purified and crude preparations obtained with mild extraction procedures. It has also been shown that the loss of growth response does not involve development of a response to the diabetogenic action of the hormone in the rat.

Fajans, Stefan S.; and Conn, Jerome W.: FURTHER STUDIES ON A TEST FOR THE "PREDICTION" OF DIABETES MELLITUS. Clin. Res. Proc. *3*:122-23, April 1955.

The purpose of this study was to determine whether one could predict which nondiabetic individuals with a family history of diabetes would eventually develop the disease. Such patients were given a cortisone-modified glucose tolerance test. Twenty-four per cent of 215 healthy relatives of diabetic patients were found to have diabetes before any prediction test was done. The remaining 76 per cent with a family history of diabetes demonstrated no abnormality of carbohydrate tolerance. But among these, 25 per cent gave a response to the cortisone-glucose tolerance test which indicated potential diabetes. Seven obese diabetics showed normal glucose tolerance tests after weight reduction. The cortisone-glucose tolerance test, however, gave a positive indication of potential diabetes in all.

It appears significant that this test is capable of separating nondiabetic relatives of diabetic patients into two groups—one which responds in the same way as diabetics and one which responds normally.

Feldman, Maurice: THE PANCREAS IN THE AGED: AN AUTOPSY STUDY. Geriatrics *10*:373-74, August 1955.

In an autopsy of 185 subjects from 75 to 100 years of age, it was found that the pancreas undergoes various cellular changes which apparently produce physiological changes in the functional mechanism. There was no significant increase in the incidence of gross pathology of the pancreas. The incidence of diabetes mellitus in the total of 1,319 consecutive adult autopsies was 10.3 per cent. Of this number, 25.5 per cent occurred in persons between 70 and 85 years of age. The incidence in 185 aged subjects from 75 to 100 was 13.5 per cent.

Fischer, Franz: RETINOPATHY AND DIABETES MELLITUS. von Graefes Arch. Ophth. *155*:567-73, 1954. (Abstracted from Am. J. Ophth. *39*:915-16, June 1955.)

The retinopathies more often occurred in patients over forty-six years of age, affected both sexes about equally, and combined more often with high blood pressure, albuminuria, functional disturbances of the kidneys, and arteriosclerosis. Retinal exudates and proliferations seemed to represent inherent diabetic factors, whereas the retinal hemorrhages might simply be facilitated by the diabetic condition.

Foreign Letters: DIETING FOR DIABETES. J.A.M.A. *158*:214-15, May 21, 1955.

The shortage of food in Finland after 1939 forced diabetics to manage on the same meager rations allotted to the rest of the population. Under a dietary much poorer in calories than that previously enjoyed, new cases of diabetes became remarkably rare; and on the whole, the disease was kept well under control. As a result of this wartime dietary being so satisfactory, there was a tendency after the war to neglect the strict prewar dietary. Both diabetics and their fellow men showed a marked gain in weight. Soon the number of new cases of diabetes rose slowly, and it became increasingly difficult to control acidosis and glycosuria.

Fridhandler, L.; and Quastel, J. H.: ABSORPTION OF SUGARS FROM ISOLATED SURVIVING INTESTINE. Arch. Biochem. *56*:412-23, June 1955.

The authors have studied the absorption of sugar from

the isolated guinea-pig small intestine. Fructose absorption is increased when its concentration is increased in the lumen. The presence of anaerobic conditions, or that of 2-4-dinitrophenol under aerobic conditions, suppresses glucose formation from fructose in the isolated intestine but does not influence the rate of absorption of fructose. Phlorhizin suppresses active glucose absorption but has no effect on fructose absorption or on glucose formation from fructose. Sucrose is absorbed passively. The authors conclude absorption is "active" and by diffusion.

Galansino, Giorgio; Weinstein, Harriet R.; Magill, Alfred M.; and Foa, Piero P.: RATS CHRONICALLY TREATED WITH GLUCAGON. Am. J. Physiol. *180*:27-30, January 1955.

Twenty-four adult rats received daily intraperitoneal injections of glucagon for periods of from 14 to 164 days. Twenty-four control rats received similar injections of saline. No significant changes were noted in glucose tolerance, insulin tolerance, glycogen content of liver, heart or gastrocnemius muscle, serum cholesterol, lipid P and lipoprotein pattern, number and appearance of A and B cells of the islets of Langerhans, and weight or morphological appearance of heart, liver, pancreas, pituitary, and adrenals.

Garb, Solomon; Penna, Mario; and Scriabine, Alexander: SPECIES DIFFERENCES IN THE UTILIZATION OF GLUCOSE FOR CONTRACTILE FORCE BY ISOLATED PERFUSED HEARTS. Am. J. Physiol. *180*:103-06, January 1955.

Experiments on isolated perfused mammalian hearts showed marked species differences in the effect of glucose on contractile force. The substrate-depleted rat heart responded to glucose with an increase equal to 50 per cent of the original force. Guinea pig, rabbit, and cat hearts gave responses of 12, 8, and 4 per cent respectively.

Goldberg, Aaron L.; and Rosenberg, William A.: NECROBIOSIS LIPOIDICA DIABETICORUM WITH INTERCAPILLARY GLOMERULOSCLEROSIS. A.M.A. Arch. Dermat. *71*:642-43, May 1955.

The authors report a case presenting the combination, not hitherto reported, of necrobiosis lipoidica diabeticorum plus intercapillary glomerulosclerosis (Kimmelstiel-Wilson syndrome) in a patient with diabetes mellitus. Spectroscopic analysis showed an excess of sodium in the tissue.

Gottfried, Sidney P.; Pope, Russell H.; Friedman, Nathan H.; Akerson, Irving B.; and DiMauro, Salvatore: LIPOPROTEIN STUDIES IN ATHEROSCLEROTIC AND LIPEMIC INDIVIDUALS BY MEANS OF PAPER ELECTROPHORESIS. Am. J. M. Sc. *229*:34-40, January 1955.

The authors report a study of total serum lipids, total cholesterol, and alpha and beta lipoproteins in 39 "normal," 8 atherosclerotic, and 17 "lipemic" men and women from 20 to 55 years of age. Repeated determinations over considerable periods of time were performed in the atherosclerotic individuals who suffered an episode of myocardial infarction, in order to correlate the blood lipid findings with the time of occurrence of the clinical episode.

Criteria for the categories "normal," "lipemic," and atherosclerotic were as follows:

"Normal" subjects were either ambulatory patients or hospitalized orthopedic cases with no clinical evidence of cardiovascular, renal, hepatic, or metabolic diseases.

"Lipemic" subjects were "normals" who were found to have a total serum lipid of over 800 mg. per 100 cc.

"Atherosclerotic" cases included patients under 55 years of age who showed no evidence of other metabolic, endocrine, or nutritional disease; who had no antecedent history of congenital, acquired, or hypertensive heart or vascular disease; and who exhibited a proved coronary thrombosis or occlusion with myocardial infarction or angina pectoris with ECG evidence of myocardial ischemia.

The normal subjects revealed no variation in the alpha lipoproteins with age or sex, the values ranging from 1.00 to 1.40. The beta lipoproteins were higher in men in their twenties than in women of the same age group, being 1.91-2.36 for the former and 1.30-2.12 for the latter.

Studies on the atherosclerotic patients were initiated as soon after a myocardial infarction as possible. Six of the eight cases revealed an elevated beta lipoprotein (as compared with normal of same age and sex group) when studies were initiated but tended to drop to normal as the interval from the time of the infarct increased. In one of the two remaining cases, the beta lipoprotein, initially normal, became elevated with the passage of time. All cases showed at least one total serum lipid about 800 mg. per 100 cc. or total cholesterol above 300 mg. per 100 cc. or both; but many of the values in the serial analyses were below these figures.

An elevated beta lipoprotein was noted in 5 of 12 lipemic men and in 2 of 5 of the women. The prognostic significance of this will be revealed by future events.

Green, Harry; Bocher, Carol A.; and Leopold, Irving H.: ANAEROBIC CARBOHYDRATE METABOLISM OF THE CRYSTALLINE LENS. I. GLUCOSE AND GLUCOSE-6-PHOSPHATE. Am. J. Ophth. *39*:106-13, February, pt. 2, 1955. (Paper presented at 23rd Meeting of the Association for Research in Ophthalmology, Inc., San Francisco, June 23-25, 1954.)

In 1928, Kronfeld and Botham first demonstrated the ability of the crystalline lens to produce lactic acid from glucose. Since then, fragmentary evidence has accumu-

lated which suggests that lens glycolysis involves intermediary phosphorylation and the participation of phosphate esters. Increased amounts of lactic acid were formed when glucose-6-phosphate, fructose-6-phosphate, or glucose-1-phosphate were substituted for glucose. The addition of hexokinase very markedly increased the formation of lactic acid.

Green, Harry; Bocher, Carol A.; and Leopold, Irving H.: ANAEROBIC CARBOHYDRATE METABOLISM OF THE CRYSTALLINE LENS. II. FRUCTOSE DIPHOSPHATE. Am. J. Ophth. 39:113-17, February, pt. 2, 1955. (Paper presented at 23rd Meeting of the Association for Research in Ophthalmology, Inc., San Francisco, June 23-25, 1954.)

The relative deficits of hexokinase and adenosine triphosphatase in lens extract were limiting factors in the production of lactic acid from glucose and glucose-6-phosphate and fructose-6-phosphate. When the glucose system was fortified with hexokinase and inorganic phosphate and the hexosemonophosphate system fortified with phosphate acceptor, adenosine diphosphate, or adenosine monophosphate, increased quantities of lactic acid were formed. The anaerobic metabolism of fructose diphosphate by an extract of rabbit lens was studied. Fructose diphosphate, with or without added inorganic phosphate, formed very little lactic acid. In the presence of a suitable phosphate acceptor, adenosine diphosphate, or adenosine monophosphate, considerable quantities of lactic acid were produced. The anaerobic utilization of glucose by lens extract follows a pathway essentially similar to that described for yeast, muscle, and other mammalian tissues.

Harris, John E.; Hauschildt, James D.; and Nordquist, Loretta T.: TRANSPORT OF GLUCOSE ACROSS THE LENS SURFACES. Am. J. Ophth. 39:161-69, February, pt. 2, 1955. (Paper presented at 23rd Meeting of the Association for Research in Ophthalmology, Inc., San Francisco, June 23-25, 1954.)

It has been observed that glucose, in sufficiently high concentrations (500 mg. per 100 cc. or more), has a deleterious effect on the transport of cations by the lens and that adenosine triphosphate, which provides the immediate energy for the phosphorylation by which glucose enters the glycolytic cycle, tends to negate these adverse effects. The lens was considered to be an excellent tissue for studies aimed at determining whether glucose crosses cellular barriers by simple diffusion or metabolic mediation or both. Studies of the accumulation of glucose within and its utilization within by the rabbit lens treated with various enzyme inhibitors have indicated that glucose does not enter the lens solely by simple diffusion but also by some active process involving metabolic mediation.

Hauschildt, James D.; Harris, John E.; and Nordquist, Loretta T.: CHANGES IN THE PHOSPHATE FRACTIONS OF THE LENS UNDER VARIOUS CONDITIONS WHICH INFLUENCE CATION TRANSPORT. Am. J. Ophth.39:155-59, February, pt. 2, 1955. (Paper presented at 23rd Meeting of the Association for Research in Ophthalmology, Inc., San Francisco, June 23-25, 1954.)

Studies of a variety of factors, including the effect of glucose and monosaccharides, enzyme inhibitors, adenosine triphosphate (ATP), oxygen, and certain metabolites of the tricarboxylic acid cycle, have indicated that the energy for active cation transport across lenticular barriers generally derives from the metabolism of carbohydrate. Phosphorus plays an essential role in carbohydrate utilization. The present report concerns the effects of some conditions known to alter cation transport upon certain phosphate fractions (inorganic, easily hydrolyzable, and organic acid-soluble [OASP] of the lens. A decrease in serum potassium and inorganic phosphate frequently occurs when carbohydrate utilization is stimulated in the intact animal. The decrease in each instance is considered to result from the migration of the ions into the cell; the phosphate accumulates as organic esters.

Hayden, Peter M.: VASCULARIZED VEIL. Am. J. Ophth. 39:742, May 1955. (Discussion at clinical meeting of Chicago Ophthmological Society, Jan. 18, 1954.)

Vascular veils within the vitreous occurs as a cardinal sign of previous occlusion. Its occurrence in diabetes, arteriosclerosis, and other senile conditions is usually indicative of vascular occlusion rather than a complication of the disease.

Iskrant, Albert P.; and Kurlander, Arnold B.: DIABETES MELLITUS MORTALITY IN THE CONTINENTAL UNITED STATES—1950. J. Chronic Dis. 1:368-80, April 1955.

In 1950, the death rate for diabetes was 16.2 per 100,000 population. The rate is highest in white females. The death rate is also higher in urban than in rural areas. The mortality varies in different states, being highest in the Northeast and North Central States and lowest in the South and West. The trend of the number of deaths and crude death rates from diabetes has been upward since 1900, with a tendency to level off in recent years.

Karvinen, Esko; Lin, T. M.; and Ivy, A. C.: EFFECT OF MINERAL OIL ON INTESTINAL ABSORPTION OF CHOLESTEROL IN THE RAT. Am. J. Physiol. 181:439-40, May 1955.

The addition of light mineral oil (U.S.P.) at a level of 6 per cent of the dry weight of the diet in rats increased the fecal excretion of endogenous cholesterol by 39 per cent when there was no cholesterol in the diet

and increased the total excretion of cholesterol by 30 per cent when cholesterol was added to the diet. It is probable that most of the increased excretion is due to the solubility of cholesterol in the mineral oil (1.1 per cent at 37°C.), although laxation is also probably concerned to some extent.

Laragh, John H.; and Capeci, Nicholas E.: EFFECT OF ADMINISTRATION OF POTASSIUM CHLORIDE ON SERUM SODIUM AND POTASSIUM CONCENTRATION. Am. J. Physiol. *180*:539-44, March 1955.

Ten metabolic balance studies were carried out on normal dogs receiving constant intake of food and water. The effect of potassium chloride feeding was compared in these dogs (1) when on a normal sodium intake, (2) after prolonged sodium restriction, and (3) after sodium depletion by peritoneal dialysis. A significant increase in the serum sodium concentration regularly occurred after the administration of KCl. This response was most pronounced in the sodium-restricted dog. The observed changes seemed best explained by postulating a release of sodium ion into the extracellular space in exchange for potassium.

No significant changes in the over-all balance of sodium and water were observed in any of these experiments after the feeding of relatively huge amounts of KCl. Potassium chloride in large dosage was not observed to be an effective diuretic in these experiments.

The sodium-depleted dog developed profound and prolonged hyperkalemia after KCl, resulting in death of one dog. This hyperkalemia was apparently not related to an incapacity for renal excretion of potassium, nor did change in body-fluid spaces seem to be a critical factor. The presence of sodium depletion per se apparently limits the capacity of the organism to remove potassium from the extracellular fluid. Hyperkalemia develops much more readily, and its adverse effect on cardiac muscle may be irreversible. In the presence of sodium depletion, the administration of potassium ion is therefore dangerous.

Lisiecka-Adamska, H.; Miratynska-Rusinowa, E.: ANGIECTASES IN DIABETICS. Klinika Oczna *24*:105-12, 1954. (Abstracted from Am. J. Ophth. *39*:271, February 1955.)

Among 667 diabetics, 195 had angiectases. In 102 of them, there were other diabetic retinal changes. There was no relation between the severity or duration of diabetes and the frequency of angiectases; they were found more frequently in nontreated or irregularly treated patients and also in younger people. High blood pressure was not considered a contributing factor.

Lundbaek, Knud: DIABETIC RETINOPATHY IN NEWLY DIAGNOSED DIABETES MELLITUS. Acta med. scandinav. *152*:53-60, July 1955.

The reported incidence of diabetic retinitis in newly diagnosed diabetes mellitus has varied from 5.8 to 15 per cent. In an analysis of 246 such cases, diabetic retinopathy was found in only 4 per cent. Careful analysis of the case histories disclosed that diabetic retinopathy in truly *recent* diabetes mellitus *may* have been present in two cases, i.e., less than 1 per cent of the patients.

Lupu, Charles I.; and Farber, Emmanuel: EFFECTS OF ETHIONINE UPON HEPATIC GLYCOGEN FORMATION FROM GLUCOSE IN INTACT RATS. Proc. Soc. Exper. Biol. & Med. *86*:701-05, August-September 1954.

The intraperitoneal injection of *dl*-ethionine produced a decrease in liver glycogen in both male and female rats given glucose by stomach tube, a decrease in liver glycogen in male and female rats given glucose subcutaneously, an increase in glucose unabsorbed from the alimentary tract in male and female rats given glucose by stomach tube, and a decrease in liver glycogen in female rats given glucose by stomach tube or subcutaneously three hours prior to the administration of ethionine. Female rats generally showed changes of greater magnitude than males under the same conditions. Methionine prevented in part some of the effects on liver glycogen but had an effect similar to ethionine on glucose absorption from the alimentary tract.

Mach, R. S.; Fabre, J.; Duckert, A.; Borth, R.; and Ducommun, P.: CLINICAL AND METABOLIC ACTION OF ALDOSTERONE (ELECTROCORTINE). Schweiz. med. Wchnschr. *84*:407-16, April 10, 1954.

After a preliminary period without therapy, two cases of Addison's disease were treated with the new adrenocortical hormone aldosterone. Within a few hours, the clinical and the electrolytical manifestations of the disease disappeared; and within a few days, even the skin pigmentations regressed, and the blood pressure became normal.

In the two patients suffering from Addison's disease, the effective dose was 150 to 200 mcg. of aldosterone per day (2.5 to 3.3 mcg. per kg. of body weight). Aldosterone seems to be 20 to 30 times more active than DOCA.

Aldosterone, like desoxycorticosterone acetate, causes sodium and chloride retention and increased potassium excretion. In the blood, a slight decrease of the potassium concentration and signs of hemodilation were observed. Aldosterone raised the blood sugar to 145 mg. per cent and suppressed the secondary hypoglycemia. One patient was relieved from pains in his knee joints by aldosterone,

but a patient with chronic progressive polyarthritis did not lose her pains when she received 400 mcg. of aldosterone during three days.

With the small dosage used, aldosterone had no effect on blood cells such as eosinophils, on nitrogen metabolism, on water load tests, or on 17-ketosteroid and formaldehydogenic corticoid levels in the urine. Contrary to DOCA, aldosterone does not cause hypertension nor abnormal water retention. (French)

McLaughlin, Charles W., Jr.; Heider, Charles F., Jr.: THE CONTINUING PROBLEM OF INFECTION AND GANGRENE IN THE DIABETIC EXTREMITY. Am. J. Surg. *89*: 964-67, 1955.

A group of 135 cases of diabetic gangrene occurring in a series of 1,912 diabetics is reviewed. The authors emphasize that good medical management and meticulous care of the extremities is most important in reducing the instance of gangrene. Close cooperation between the intern and the surgeon is needed in order to reduce mortality and length of hospitalization. Prompt radical surgery has reduced the mortality and length of hospitalization. The authors feel that lumbar sympathectomy may be of value in selected cases.

Magid, George J.; and Steenrod, William J., Jr.: INTRAVENOUS FRUCTOSE IN THE MANAGEMENT OF DIABETIC EMERGENCIES. Bull. Mason Clin. *9*:10-15, March 1955.

The authors present a brief review of the metabolism of fructose and present possible clincial uses for this sugar.

Margolis, Harry M.; Barr, James H., Jr.; Stolzer, Bertrand L.; Eisenbeis, Carl H., Jr.; and Martz, E. Wayne, Jr.: EFFECTS OF PREDNISONE (METICORTEN) ON MANIFESTATIONS OF RHEUMATOID ARTHRITIS. REPORT OF EARLY CLINICAL OBSERVATIONS. J.A.M.A. *158*:454-58, June 11, 1955.

Observations concerning the diabetogenic properties of prednisone (Meticorten) suggest that this aspect of metabolism will require close scrutiny. On the other hand, the favorable effect of prednisone on the severe anemia of some patients with rheumatoid arthritis points to the need for careful study of the effect of this hormone on erythropoiesis and on possible modification of the "hemolytic" factor in this disease.

Nath, M. C.; and Chakrabarti, C. H.: BIOSYNTHESIS OF ASCORBIC ACID AND PREVENTION OF GLYCOGEN DEPLETION IN LIVER AND MUSCLE. Proc. Soc. Exper. Biol. Med. *86*:851-54, August-September 1954.

The intramuscular injection into rats of sodium acetoacetate in low concentrations (up to 200 mg. per kg.) caused an increase in blood ascorbic acid over a 4-hour period but did not cause any change in blood sugar levels or liver and muscle glycogen concentrations. At higher concentrations of acetoacetate (600 mg. per kg.), no such rise in ascorbic acid was found; and repeated daily injections resulted finally in elevated blood sugar levels and depletion of liver and muscle glycogen. Sodium β-hydroxybutyrate, when given in smaller daily doses (50 mg. per kg.), also failed to produce an increase in blood ascorbic acid. In rabbits, neither the injection of acetoacetate nor of β-hydroxybutyrate resulted in any increase in blood ascorbic acid. The authors attempt to correlate the failure of the blood ascorbic acid to rise after the injection of ketone bodies with the development of the diabetic state.

Nieman, C.: INFLUENCE OF DIETARY FAT ON INCIDENCE OF ALLOXAN DIABETES IN GROWING RATS. Am. J. Physiol. *181*:183-86, April 1955.

Young rats fed adequate rations containing 10 or 20 per cent fat were rendered diabetic by one or two subcutaneous injections of 200 mg. alloxan per kg. of body weight. When the diet was composed of either 10 or 20 per cent fat, consisting either of butter fat (11.4 per cent short-chain fatty acids; iodine number 36.2) or vitamin-enriched peanut oil (no short-chain fatty acids; iodine number 96.8), the diabetogenic and toxic action of the drug was influenced by the nature of the dietary fat, as judged from diabetic incidence and mortality rate. The peanut-oil-fed rats exhibited twice as great an incidence of severe diabetes and three times as great a mortality rate. Apparently, the favorable influence of butter fat is related to the greater content of saturated fatty acids. In alloxan-diabetic animals, the urinary excretion of riboflavin was markedly increased.

Nordman, J.; Mandel, P.; and Achard, M.: INHIBITION OF SUGAR METABOLISM IN THE LENS. Brit. J. Ophth. *38*:673-79, November 1954. (Abstracted from Am. J. Ophth. *39*:771-72, May 1955.)

It is indicated that interference with sugar metabolism is always followed by some cataractous changes.

O'Brien, J. Miles: PRESENT STATUS OF CLINICAL ELECTRORETINOGRAPHY. Am. J. Ophth. *39*:245-47, February 1955. (Presented at Yale University Clinical Conferences, Nov. 13, 1953.)

Electroretinography records changes in the electrical potential of the human eye when exposed to light. Any major alteration in retinal circulation affects the electroretinogram. Diabetic retinal involvement, unless very extensive, has shown no changes in the electroretinogram.

Patterson, John W.: EFFECT OF BLOOD SUPPLY ON THE DEVELOPMENT OF CATARACTS. Am. J. Physiol. *180*: 495-97, March 1955.

The initial cataract in galactose-fed rats is just as

likely to appear in one eye as in the other. The left side is favored to a slight extent. Following unilateral carotid ligation, galactose-fed rats develop cataracts on the side with the better blood supply and, hence, the higher galactose supply. This is interpreted as indicating that galactose produces cataracts by acting at the level of the eye. The initial cataract in diabetic rats appears on the left side about half of the time. Changing the blood supply to the eyes by unilateral carotid ligation does not affect the development of diabetic cataracts. In this way diabetic cataracts are different from galactose cataracts. It is suggested that high glucose levels, therefore, are not directly responsible for cataract production and that cataracts may be the result of a lack of insulin.

Perry, W. F.; and Bowen, Helen F.: INCORPORATION OF ACETATE INTO FATTY ACID BY LIVER SLICES OF ADRENALECTOMIZED RATS. Am. J. Physiol. *180*:21-22, January 1955.

The incorporation of 2-C^{14} acetate into fatty acids by liver slices of fasted, force-fed and ad-libitum-fed male adrenalectomized rats has been examined.

Compared with similarly fed intact rats, such liver slices incorporated less acetate into fatty acids on all regimens.

Queries and Minor Notes: CANCER AND DIABETES. J.A.M.A. *158*:802, July 2, 1955.

The incidence of cancer in the diabetic population has been shown to be significantly increased. Statistically, the risk of cancer in the diabetic population was as much as eight times greater than in the nondiabetic population. Thus, there would appear to be no basis for the inference that ketosis or acidosis is a guard against carcinogenesis.

Queries and Minor Notes: CHRONIC PANCREATITIS. J.A.M.A. *158*:624, June 18, 1955.

The most positive means of diagnosing pancreatic calculi is by X-ray examination of the abdomen centering over the pancreas. In about 10 to 20 per cent of patients with chronic pancreatitis, calculi will be present. The most frequently used test is determination of serum amylase, which should be over 300 mg. per 100 cc. on at least two different occasions in association with acute abdominal pain. Some patients with chronic pancreatitis develop diabetes; therefore, a glucose tolerance test or repeated daily urinalysis is useful.

Queries and Minor Notes: DIABETIC RETINITIS. J.A.M.A. *157*:778, Feb. 26, 1955.

The best possible control of diabetes appears to be indicated in the management of diabetic patients with retinopathy. In spite of the fact that the urine remains sugar free, insulin therapy may be used advantageously. Any one of the long-acting or intermediate-acting insulins could be administered before breakfast, a safe starting dose being 12 units. A 24-hour estimation of the glucose excreted would be of greater value than the examination of a single specimen. Although many disagree in the use of rutin, it could be prescribed in large doses, such as 1,000 mg. a day, and in addition the patient could receive vitamin C.

Queries and Minor Notes: METABOLISM OF GLYCERIN. J.A.M.A. *158*:521, June 11, 1955.

Glycerin is absorbed and metabolized by man. After absorption, it is converted to glucose and is used as such. Weight for weight, it has roughly the same caloric value as glucose. Its normal structure is much like that of dextrose; its caloric value, gram for gram, is about the same as that of dextrose—4 calories per gram. Like dextrose, also, it is either oxidized to carbon dioxide and water or converted to fat. The use of glycerin as a sweetening agent in diabetes is not advantageous because its use in severe diabetes is no more satisfactory than that of sugar.

Queries and Minor Notes: "SPOT" WEIGHT REDUCTION. J.A.M.A. *158*:150, May 14, 1955.

The erroneous belief is widespread among lay persons and enthusiastically promoted by various commercial interests that weight reduction in special areas of the body is possible. This is sometimes referred to as "spot" reduction. There is no physiological basis for such an assumption and no clinical evidence that this can ever be accomplished.

Queries and Minor Notes: WEIGHT REDUCTION. J.A.M.A. *158*:706, June 25, 1955.

Any effect of fluid restriction or low-salt regimens on weight reduction of the obese patient is due entirely to the influence of such regimens on water loss. They do not promote the consumption of the excessive tissue fat and, accordingly, are not effective in the treatment of obesity.

Richardson, G. O.; Snaith, Linton; and Sibley, J. C.: PREGNANCY COMPLICATED BY DIABETES. J. Obst. & Gynaec. Brit. Emp. 62:262-65, April 1955.

The author reviews the management of the pregnant diabetic. Careful control of the diabetes, early delivery, and competent neonatal care are stressed. The question of the value of supplemental hormonal therapy remains unsolved.

Robinson, Harry M., Jr.: PREDNISONE IN TREATMENT OF SELECTED DERMATOSES. PRELIMINARY REPORT. J.A.M.A. *158*:473-75, June 11, 1955.

No significant alteration was noted in the blood sodium, potassium, or nitrogen levels during the course of prednisone therapy in any of these patients. No change was noted in the albumin-globulin ratio in any of these individuals during the course of treatment. None of the patients developed glucosuria, and the blood glucose levels remained stabilized.

Rodriguez, Ricardo R.: CATARACT FORMATION AND DIABETES CONTROL IN THE RAT. Arch. oftal. Buenos Aires 29:207-12, April 1954. (Abstracted from Am. J. Ophth. 39:462, March 1955.)

The frequency with which specifically diabetic cataract formation occurs is closely related to the severity of the condition, the type of diet, and the adequacy of insulin treatment. It depends basically on the levels at which the glycemia is maintained. On the other hand, evidence is provided to show that the younger the animal and the higher the blood sugar content, the shorter the latent period which precedes cataract formation.

Rohse, Wayne G.; and Searle, Gordon W.: ABSORPTION OF CHOLINE FROM INTESTINAL LOOPS IN DOGS. Am. J. Physiol. *181*:207-09, April 1955.

The authors report that in the acute and chronic dog, excised ileal loops effectively absorb choline chloride, as evidenced by both absorption rates and by parasympathomimetic effects exhibited after the administration of large doses of choline chloride.

Ryle, A. P.; Sanger, F.; Smith, L. F.; and Kitai, Ruth: THE DISULPHIDE BONDS OF INSULIN. Biochem. J. 60: 541-56, August 1955.

Highly purified cattle insulin was partially hydrolysed with chymotrypsin, with a crude pancreatic extract, and with acid without breaking the disulphide bonds. Cystine-containing peptides in the hydrolysates were separated and their structures determined after oxidation to cysteic acid peptides. Separations were effected using paper iontophoresis at high potential gradients in pyridine-acetic acid. The distribution of the disulphide bonds of cattle insulin was deduced from the structure of the cystine dipeptides; these are illustrated in the publication together with the arrangement of the amino acids in the two polypeptide chains of the insulin molecule.

Schor, Isaias: INSULIN. Orientación Médica *4*:302-03, April 15, 1955. (Thesis for doctorate).

The author reviews the physical and chemical properties of insulin and discusses the possible mechanisms of its action.

Shapiro, Seymour L.; and Freedman, Louis: EFFECT OF ESSENTIAL UNSATURATED FATTY ACIDS AND METHIONINE ON HYPERCHOLESTEREMIA. Am. J. Physiol *181*: 441-45, May 1955.

Unsaturated fatty acids serve a noncalorigenic function and exert a protective action against hypercholesteremia when they constitute approximately 2.5 per cent by weight of the total diet. The use of fats containing these acids beyond caloric levels, where they comprise 10 to 15 per cent by weight of the diet, breaks their protective action, introduces a typically calorigenic contribution to the diet, and promotes hypercholesteremia.

Sheely, R. F.; Johnson, C. H.; Baker, J.J.; and Harbaugh, Rodney: EFFECT OF CORTISONE AND HYDROCORTISONE IN HEMIPLEGIA AFTER CEREBRAL INFARCTION. I. PRELIMINARY REPORT, WITH SPECIAL REFERENCE TO SPASTICITY. J.A.M.A. *158*:803-06, July 9, 1955.

Four patients with residual spastic defects following cerebral infarction were treated with hydrocortisone (three cases) and cortisone (one case) in conjunction with physical therapeutic measures. Following the use of corticosteroids, a marked decrease in painful spasticity was observed.

Caution must be exercised to avoid haphazard use of corticosteroids in the geriatric age group, because of the high incidence of hypertension, diabetes mellitus, dyspepsia, and renal or liver disease.

During the period of administration of the corticosteroids, there were no adverse effects noted on existing hypertension, glucose metabolism, or water or electrolyte balance.

Shuman, Charles R.; Kemp, Robert L.; Coyne, Richard; and Wohl, Michael G.: SORBITOL FEEDING IN DIABETIC PATIENTS. Clin. Res. Proc. 3:123, April 1955.

Sorbitol, a sugar alcohol prepared for commercial use by the dehydrogenation of glucose, is being used as a sweetening agent in many diabetic foods. This study demonstrates that the addition of sorbitol to a controlled diet produces no significant alteration in the diurnal blood glucose values nor in the quantity of urine glucose excretion.

Possibly this may be attributable to the slow absorption of sorbitol in the gastrointestinal tract and its relatively slow conversion to glycogen through fructose.

Simmons, Daniel H.; Harvey, Rodney B.; and Hoshiko, T.: ROLE OF ADRENAL AND HYPOPHYSIS IN REGULATIN OF SODIUM EXCRETION. Am. J. Physiol. *181*:379-89, May 1955.

A previously described method of estimating renal "sodium-retaining activity" in the dog is used to compare the effect of chronic DCA administration and total hypophysectomy with alterations in sodium intake on this activity. Injection of large doses of DCA is not found to simulate the effect of a decrease in sodium intake.

Hypophysectomy produces minor alterations in renal sodium-retaining activity which are not comparable in degree to those resulting from the extreme changes in sodium intake used in this study.

Balance studies indicate that the response of the dog to extreme alterations in sodium intake is only slightly affected by total hypophysectomy.

These results are most consistent with the conclusion that neither the adrenal cortex nor the pituitary is necessary for the regulation of sodium excretion, although either may have nonregulatory effects.

Spitzer, John J.: Removal and Mobilization of Lipids in Normal and Hepatectomized Dogs. Am. J. Physiol. *181*:83-88, April 1955.

The mechanism of the action of injected heparin or protamine was investigated in normal and in functionally hepatectomized lipemic dogs by ligation of the hepatic artery and portal vein. Visible changes in the femoral artery and in the vein after the injection of either were very similar and occurred simultaneously. The injection of protamine into thoracic-duct-cannulated lipemic animals, with or without hepatectomy, caused an increase in lipemia which was less consistent and less marked than in normal lipemic animals. Hepatectomy produced a dramatic increase of visible lipemia which was significantly higher in the femoral artery than in the vein. This increased lipemia could be cleared by heparin and increased again by protamine. The last increase was greater and more rapid in the femoral artery than in the vein. Blood lipid determinations by chemical methods and by feeding Sudan IV-stained fats and determining the Sudan IV content of the blood showed that changes in visible lipemia generally are accompanied by similar chemical changes. They indicate that the lipemic response produced by heparin or protamine involves the removal and mobilization of lipids. Heparin produces an enzyme-clearing factor which induces transformation and breakdown of lipoproteins and increases the removal of lipids from the blood to the tissues. Possible explanations for the lipemia-increasing effect of protamine are that (1) it antagonizes the endogenous clearing factor during fat metabolism and (2) it mobilizes lipids from fat depots.

Sprenger, Lucille A.: Recognition and Diagnosis of Diabetes Mellitus. Illinois M. J. *107*:240-44, May 1955.

Diabetes detection drives have been emphasized in recent years. Their importance is obvious. Their purpose is not only the detection of new cases; they serve also in the education of laymen and physicians. Too many physicians are still employing a fasting blood sugar or urinalysis alone as a diagnostic procedure for diabetes. Attention should be given to cases of early and mild diabetes which may escape detection if tests are made only in the fasting state.

If physicians are aware of the symptoms and signs of diabetes and of the need for definitive diagnostic procedures, recognition and diagnosis will assume their rightful importance.

Spurr, Charles L.; Waller, Jester J., Jr.; and Stribling, Samuel H.: The Effect of Various Disease States on the Intravenous Glucose Tolerance and Glucose Insulin Tolerance Test. Clin. Res. Proc. *3*:122, April 1955.

During long-term corticotropin and steroid therapy, the glucose tolerance test was diabetic in 57 per cent and the insulin response subnormal in 43 per cent. The disappearance rates in normals were found to be constant and reproducible, and there were statistically significant changes characteristic of each disease state. Interpretation by this method allows more accurate differentiation between normal and borderline states of glucose utilization and insulin response.

Steinmann, B.; and Widmer, J.: Function Test of Pancreas. Schweiz. med. Wchnschr. *85*:411-16, April 30, 1955. (Abstracted from J.A.M.A. *158*:980, July 16, 1955.)

Abnormal serum diastase values also were found in patients with various abdominal disorders, bronchial asthma during the free interval between attacks, diabetes mellitus, and multiple sclerosis.

Swell, Leon; Boiter, T. A.; Field, Henry, Jr.; and Treadwell, C. R.: Absorption of Dietary Cholesterol Esters. Am. J. Physiol. *180*:129-32, January 1955.

Rats were fed synthetic high-fat diets containing 2 per cent of either cholesterol, cholesterol butyrate, cholesterol oleate, or cholesterol linoleate, both with and without bile salts. Rats fed cholesterol and cholesterol butyrate had a greater increase of their cholesterol than those fed cholesterol oleate or cholesterol linoleate. The elevation of the blood cholesterol was greater when sodium taurocholate was included in the diet. The observed differences in the elevations of the blood cholesterol in rats fed free cholesterol and the esters may be related to in vitro observations, showing that cholesterol butyrate is split rapidly, whereas cholesterol oleate and linoleate are split at a slower rate. The data suggest that cholesterol must be in the free form before it can be absorbed.

Swell, Leon; Flick, D. F.; Field, Henry, Jr.; and Treadwell, C. R.: Role of Fat and Fatty Acid in Absorption of Dietary Cholesterol. Am. J. Physiol. *180*: 124-28, January 1955.

Cholesterol-free diets containing soybean oil hydrogenated to varying degrees were fed to rats. It was found that the level of the blood cholesterol varied with the iodine number of the fat and that the highest degree of unsaturation produced the highest blood cholesterol level. Free fatty acids were found to be more effective in raising the blood cholesterol level than neutral fats. The differences between the various fats and fatty acids may be related to the in vitro observations, showing that cholesterol is esterified more rapidly with fatty acids than with neutral fat in the pancreatic cholesterol esterase system. It was also observed that fat need not be present in the diet for the absorption of dietary cholesterol, provided a sufficient amount of bile salts is present; the fatty acid necessary for esterification can come from endogenous sources. It is suggested that dietary fat serves a dual purpose: (a) It stimulates the flow of bile necessary for cholesterol esterase activity, and (b) it provides the fatty acid necessary for cholesterol esterification.

Swoboda, W.; and Zweymüller, E.: EXPERIENCES WITH NEW PROLONGED-ACTING INSULINS IN CHILDREN WITH DIABETES MELLITUS. Schweiz. med. Wchnschr. 85:231-37, March 5, 1955.

Thirty diabetics, aged 3 to 15 years, were treated with insulin zinc suspensions (Novo lente, Semilente, and Ultralente insulins). The period of observation was 3 to 18 months. A good control of the diabetes was attempted by the combination of insulin and weighed diet.

In 9 patients, who had never previously had insulin, one morning injection of insulin Lente gave satisfactory results. Of the 21 patients who had had other insulins before, ⅓ reacted well to insulin Lente and ⅓ needed individually adjusted mixtures of insulin Semilente and Ultralente; but in another third (brittle cases), it proved impossible to get a sufficient control by one daily injection of zinc suspensions.

Tepperman, Helen M.; and Tepperman, Jay: KETOGENESIS IN RATS ON HIGH CARBOHYDRATE AND HIGH FAT DIETS. Am. J. Physiol. *180*:511-18, March 1955.

Rats adapted to synthetic, isocaloric high-carbohydrate and high-fat diets show the following differences in blood ketone concentration: In the fed state, the blood ketone concentration of the fat-fed animals is significantly higher than that of the carbohydrate-fed rats; after a 24-hour fast, the reverse is true, so that the change in ketone concentration on fasting is much higher in the carbohydrate-fed animals than it is in the fat-fed ones. Surviving liver slices of fat-diet-adapted animals in the fed state make more ketone bodies than do comparable slices of carbohydrate controls. Slices obtained from 24-hour-fasted fat-fed rats make significantly fewer ketone bodies than those obtained from carbohydrate controls. On octanoate addition, there is evidence of neither diminished nor enhanced octanoic-acid-oxidizing capacity in the "fat-fed" livers. Washed liver particles from livers of fat-fed rats consistently show diminished capacity to oxidize octanoate but no impairment in oxidation of ketoglutarate. There is evidence that at least part of the "defect" in octanoate-oxidizing capacity of the particles obtained from "fat-fed" livers may be related to a less than optimal concentration of Krebs cycle intermediates in these livers. Fortified whole homogenates prepared from the two types of livers can be differentiated from one another by (a) an increased production of ketone bodies by the homogenates of the fat-fed rats and (b) by a smaller increment in both oxygen consumption and ketone production on octanoate addition in the same homogenates.

An attempt is made to relate the experimental findings in the intact animal with those seen in the slice and in reconstructed cell-free systems.

Tomlinson, B. E.: FATAL HYPOGLYCAEMIA IN EARLY NON-ICTERIC INFECTIVE HEPATITIS. Lancet *1*:1300-02, June 1955.

The author reports the case of a six-year-old girl who died in hypoglycemia with a blood sugar of 15 mg. At autopsy, the liver showed early infectious hepatitis with massive fatty infiltration.

VanArsdel, P. P., Jr.; Tomizawa, H. H.; and Williams, R. H.: INFLUENCE OF HYPERGLYCEMIC FACTOR (GLUCAGON) ON 17-HYDROXYSTEROIDS IN PLASMA AND URINE OF MAN. Proc. Soc. Exper. Biol. & Med. *86*:844-46, August-September 1954.

Plasma 17-hydroxysteroid levels and urinary 17-hydroxysteroid excretion rates were observed in eight normal humans before, during, and after the intravenous administration of the purified hyperglycemic factor. There were no significant changes in plasma values, but some patients showed elevation in urinary excretion of steroids, apparently related to the degree of stress incurred. By these methods, no direct action of hyperglycemic factor on the adrenal cortex was observed.

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WINNERS OF THE THIRD MEDICAL STUDENT-INTERN ESSAY CONTEST

The Editorial Board of DIABETES takes great pleasure in announcing the winners of the 1955 contest for the best papers in the field of diabetes written by medical students, interns or physicians within two years of graduation from medical school. Winner of the $250 award for the best paper reporting original work, made possible through the generosity of the St. Louis Diabetes Association, is Samuel S. Koide, M.D., of Northwestern University Medical School, Chicago, Illinois. His paper, entitled "Lipid Metabolism in Diabetes," was judged the outstanding contribution of the contest.

Arthur Baitch, M.D., U.S. Air Force School of Aviation Medicine, Randolph Air Force Base, Texas, was awarded the $50 prize for the best review article submitted in the contest. His paper was entitled "The Significance of the Hyperglycemic Factor in Diabetes Mellitus."

C. E. Schorer, M.D., Receiving Hospital, Detroit, Michigan, received Honorable Mention for his paper "The Pathological Physiology of 'Brittle Diabetes': A Review of Recent Studies." He was awarded a one-year subscription to DIABETES for Volume 4, 1955.

Samuel S. Koide, M.D., was graduated from the University of Hawaii in 1945, and served in the U. S. Army during World War II as an Infantry and Intelligence Officer. After receiving his M.D. degree from Northwestern University Medical School in 1953, he served an internship at Cook County Hospital, Chicago, Illinois. He obtained his M.S. degree from the Department of Biochemistry, Northwestern University, in 1954, and attended the Biochemistry Department of Columbia University as a graduate student in 1955. At present a student in the Biochemistry Department at Northwestern University, he plans eventually to specialize in internal medicine. Dr. Koide is a member of Alpha Omega Alpha. His publications include "Effects of Eck Fistula Formation on Alloxan Diabetic Dogs," with Dr. Smith Freeman, and his Master's Thesis entitled "Extraction, Hydrogenation, and Monolayer Film Study of Plasma Fatty Acids and Cholesterol."

SAMUEL S. KOIDE, M.D.

Arthur Baitch, M.D., received his B.S. degree from the University of Maryland at College Park, Maryland, and the degree of M.D. from the University of Maryland School of Medicine in 1954. He took a medical externship and then a rotating internship at the Sinai Hospital of Baltimore. It is the policy of the Department of Pathology at Sinai, under the direction of Dr. Tobias Weinberg, to encourage research among the intern staff, each intern being given the opportunity to present his paper during the year. Dr. Baitch's prize-winning paper was prepared under this program. Following internship, Dr. Baitch was a resident in Psychosomatic Medicine at the University Hospital Psychiatric Institute in Baltimore until his entrance into the Air Force. He is 26 years old, married, and plans further residency training before entering general practice.

C. E. Schorer, M.D., originally from Sauk City, Wisconsin, received his B.A. degree from the University of Wisconsin in 1939, his M.A. and Ph.D. degrees in English from the University of Chicago in 1941 and 1948; and the degree of M.D. from the University of Wisconsin in 1955. During World War II he was a Captain in the U.S. Air Force. At present, Dr. Schorer is an intern at Receiving Hospital, Detroit, Michigan.

Members of the American Diabetes Association and subscribers to DIABETES are reminded that there is now being held a fourth Medical Student-Intern Essay Contest open to medical students, interns and physicians within two years after their graduation from medical school. Association members are requested to encourage medical students and interns in their schools and hospitals to enter the contest. Contestants may choose any subject relating to diabetes and basic metabolic problems.

Manuscripts, typewritten with double-spacing, should be submitted to the Editorial Office of DIABETES, *The Journal of the American Diabetes Association,* 1 East 45th St., New York 17, N. Y. The essays will be reviewed by members of the Editorial Board, who, in selecting the best papers, will consider both the value of the material and the method of presentation.

A prize of $250 to the author or authors of the best paper reporting original work, whether laboratory investigation or clinical observation, has been made possible once again by the kindness of the St. Louis Diabetes Association. An award of $50 for the best review article or case report will also be included in the year's prizes.

SIXTEENTH ANNUAL MEETING

Chicago will be the site of the next Annual Meeting of the American Diabetes Association, to be held June 9-10, 1956, prior to the Annual Session of the American Medical Association, June 11-15. ADA groups scheduled to convene before the Annual Meeting include: Committees, June 6 and 7; Council, June 8; Board of Governors, June 8-9; Assembly of Delegates, June 9.

Members who wish to attend the Annual Meeting are urged to make their reservations immediately. The Drake will serve as headquarters hotel, and a number of individual rooms are available. An announcement of the meeting, dated Nov. 11, 1955, together with a hotel reservation card, has been sent to all members of the Association, who are urged to make their reservations promptly. It is essential that members fill out and send directly to The Drake the reservation card which accompanies the announcement. Additional reservation cards may be secured by writing to the National Office.

SCIENTIFIC PROGRAM

There will not be a Joint Meeting with The Endocrine Society this year. The first Scientific Session will be held Saturday morning, June 9, and the other Scientific Sessions will be held Sunday morning and afternoon, June 10.

FIFTH POSTGRADUATE COURSE

The American Diabetes Association will hold its Fifth Postgraduate Course in diabetes and basic metabolic problems Wednesday through Friday, Jan. 23-25, 1957, at the Ohio State Health Center, Columbus, Ohio, under the direction of George J. Hamwi, M.D.

NEW MEMBERS

ACTIVE

The following were elected as of Jan. 1 and Feb. 1, 1956:

California	
Berman, Eugene Ebert	Los Angeles
Nerlich, William Edward	Los Angeles
Place, Virgil Alan	Modesto
Ritter, Emil Richard	Arcadia
Connecticut	
Leeds, William G.	West Hartford
Georgia	
Ferris, Harold Aaron	Atlanta
Illinois	
Griffin, Joe Jinnett	Urbana
Indiana	
Bolin, Robert C.	Lafayette
Kansas	
Barker, Benjamin Wm.	Wichita

Louisiana	
Chastant, Harold Paul	Lafayette
Gulotta, Carl J.	New Orleans
Rosen, Isadore I.	Amite
Maryland	
Brown, Ernest C., Jr.	Baltimore
Massachusetts	
Jackson, James H.	Brookline
Minnesota	
Greenwold, Warren Eldon	Rochester
Kuwayti, Kamal	Rochester
Scholz, Donald A.	Rochester
New Jersey	
Gras, Alfred Edward	Newark
New York	
Hoffman, Harry	Monroe
Liesenbein, William H.	Poughkeepsie
Zarowitz, Harold	Brooklyn
Ohio	
Cotton, Claire Eugene	Cleveland
Goldberg, Robert F.	Columbus
Newill, Vaun Archie	Cleveland
Tretbar, Harvey Adrian	Cleveland
Pennsylvania	
Wolfe, Sidney M.	Philadelphia
Texas	
Dewlett, Hal Joseph	Dallas
Flohr, Leonard J., Jr.	Dallas
Giles, Robert Byron	Dallas
Hawkins, Hubert F.	Dallas
Hayes, Elmer R.	Dallas
Krakusin, Jacob S.	Dallas
Ogle, Joseph Craft	Dallas
Potts, William Henry	Dallas

Other Countries

Cuba	
Toca, Ruben Lopez	Havana
England	
Lister, John	London
Hawaii	
Sloan, Norman R.	Honolulu

ASSOCIATE

The following were elected as of Jan. 1 and Feb. 1, 1956:

Connecticut	
Sayers, Gloria E.	West Hartford
New Jersey	
Robison, Charles J.	Newark

News of Affiliate Associations

The NEW ENGLAND DIABETES ASSOCIATION held a clinical meeting at the New England Deaconess Hospital in Boston on Oct. 25, 1955. The speakers included Herman B. Chase, M.D., Professor of Biology at Brown University, Providence, Rhode Island, whose subject was "Inherited Insulin Resistance in Animals," and Russell J. Barrnett, M.D., Assistant Professor of Anatomy at Harvard Medical School, who spoke on "Histochemical Demonstration of Insulin."

Harry Blotner, M.D., the organization's president, announced plans for the annual Diabetes Fair held during Diabetes Week in Boston.

The NEW JERSEY DIABETES ASSOCIATION held its third Annual Symposium on Diabetes Mellitus in Newark, New Jersey, on Oct. 26, 1955, in cooperation with the New Jersey State Department of Health. Louis Grunt, M.D., presided as Session Chairman of Part I. The program opened with greetings by Everett O. Bauman, M.D., President. After introductory remarks by Daniel Bergsma, M.D., M.P.H., State Commissioner of Health, the following talks were given: "The Responsibilities of the Patient, Physician and Community in Long Term Diabetes Control," by Arthur Krosnick, M.D., Coordinator, Diabetes Control Program, State Department of Health; "Electrolyte Imbalance in Diabetic Acidosis," by John P. Peters, M.D., Professor of Medicine, Yale University School of Medicine; "Newer Concepts of Carbohydrate Metabolism in Diabetes Mellitus," by DeWitt Stetten, Jr., M.D., Ph.D., Associate Director in Charge of Research, National Institutes of Health.

Otto Brandman, M.D., was Session Chairman for Part II of the program. Thomas H. McGavack, M.D., Professor of Clinical Medicine, New York Medical College, spoke on "Hormonal Derangement in Diabetes Mellitus"; Garfield G. Duncan, M.D., Clinical Professor of Medicine, Jefferson Medical College of Philadelphia, on "Practical Aspects of Management in Diabetes Mellitus"; and David Adlersberg, M.D., Assistant Clinical Professor of Medicine, Columbia University College of Physicians and Surgeons, on "Degenerative Vascular Diseases in Diabetes Mellitus."

The NIAGARA FALLS DIABETES ASSOCIATION (Clinical Society) held a dinner meeting, attended by 114 physicians, on Nov. 9, 1955. Howard F. Root, M.D., Boston, reviewed recent advances in diabetes and de-

scribed the Second Congress of the International Diabetes Federation held in Cambridge, England, July 4-8, 1955. Following the dinner, Dr. Root addressed a public meeting attended by 350 persons. His talk was followed by a question period.

The TEXAS DIABETES ASSOCIATION will hold its Annual Meeting in Galveston April 21, 1956, immediately preceding the Meeting of the Texas Medical Association. F. Raymond Keating, M.D., of the Mayo Clinic, will be guest speaker.

News Notes

WILDER FELLOWSHIP AWARD

The second National Vitamin Foundation—Russell M. Wilder Fellowship to be granted by The National Vitamin Foundation was awarded to Leslie T. Webster, Jr., M.D., of Western Reserve University, Cleveland, Ohio. The fellowship is for three years beginning Jan. 1, 1956, and is worth $15,000. It was established in 1953 to express appreciation to Dr. Wilder, of the Mayo Clinic, for his more than forty years of devoted service and significant contributions to medicine and public health, and particularly for his leadership in advancing our knowledge of diseases of metabolism and nutrition.

GENETICS CONGRESS

The First International Congress of Human Genetics will be held in Copenhagen, Denmark, Aug. 1-6, 1956. Any person interested in the subject of human genetics and especially of medical genetics is invited to take part in the Congress. For information, write to The University Institute for Human Genetics, 14, Tagensvej, Copenhagen, N., Denmark.

FIRST INTERNATIONAL MEETING ON DEGENERATIVE HEART DISEASE

A Study Group on Atherosclerosis, the first of its kind to be convened by the World Health Organization, met in Geneva, Switzerland, Nov. 7-11, 1955, with the participation of twelve specialists from France, Great Britain, Japan, the Netherlands, Sweden and the United States. The WHO Study Group included experts in epidemiology, statistics, public health, cardiology, pathology, physiology, biochemistry and nutrition.

PERSONALS

EDWARD L. BORTZ, M.D., and HENRY B. MULHOLLAND, M.D., have been appointed members of an Editorial Committee of the Council on Medical Service of the American Medical Association which will publish the *Chronic Illness News Letter* beginning with the February 1956 issue. The magazine was formerly published by the Commission on Chronic Illness, an independent national agency founded by the American Hospital Association, American Medical Association, American Public Health Association, and the American Public Welfare Association.

OBITUARIES

GORDON W. RALEIGH, M.D., Evanston, Illinois, died April 13, 1955, while at work in the laboratory at the Evanston Hospital, according to information received from Lowell D. Snorf, M.D. Dr. Raleigh was born in Salt Lake City, Utah, on May 18, 1913. He received the following degrees: A.B., University of Utah, 1936; M.B. (cum Laude), Northwestern University Medical School, 1941; M.D., Northwestern University Medical School, 1942; M.S. (Pathology), Northwestern University Medical School, 1947. Much of his medical training was at Evanston Hospital where he served as an intern from 1941 to 1942; resident in pathology from 1942 to 1943; and resident in medicine in 1947.

In 1943 he entered the army of the United States where he attained the rank of Major, and in this year was assigned to the Army Medical School. From 1944 to 1946 Dr. Raleigh served as Ward Officer and Chief of Sections in General Hospitals in Europe. While stationed in England he was elected a Fellow, Royal Society of Medicine (London). He was certified by the American Board of Internal Medicine in 1948, during which year he also started private practice at Evanston Hospital on the Attending Staff. At Northwestern University Medical School, Dr. Raleigh served as Director of the Graduate Division from 1949 to 1954, and was appointed an Assistant Professor of Medicine in 1954. A member of the American Diabetes Association since 1949, Dr. Raleigh was a Fellow of the American College of Physicians, and a member of the American Association for the Advancement of Science and The Endocrine Society. He is survived by his wife and daughter.